METCHNIKOFF IN HIS LABORATORY

Discoverers for Medicine

BY

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NEW HAVEN

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To Edna

My best friend and
most lenient critic

"Medicine . . . learned . . . from a Jesuit how to cure ague, from a friar how to cut for stone, from a soldier how to treat gout, from a sailor how to keep off scurvy, from a postmaster how to sound the Eustachian tube, from a dairy maid how to prevent smallpox, and from an old market woman how to catch the itch insect."

OLIVER WENDELL HOLMES

PREFACE

IF the professional historian is so dependent on his forerunners, how much more helpless would the amateur be without similar aid. The writing of the present book would have been impossible save for the diligence of those who patiently assembled and set down the material on which it is based.

But there are still other debts to be acknowledged. Dr. Edward B. Krumbhaar, Professor of Pathology at the University of Pennsylvania, examined the manuscript in its entirety, while Dr. Bernard S. Oppenheimer, Consulting Physician to Mount Sinai Hospital, New York; Dr. Walter S. Root, Associate Professor of Physiology at the College of Physicians and Surgeons, New York; and Dr. DeGraaf Woodman, Associate Clinical Professor of Otolaryngology there, read the chapters relating to their several specialties. If despite all their care the book contain errors, these are chargeable to the author alone.

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list of those who have thus given permission is to be added The Historical Society of Pennsylvania.

The omission of Pasteur and the Curies from the account that follows is due to no oversight. They have already had their hour on page and screen.

The author has profited throughout by the advice and assistance of the staff of the Yale University Press.

W.H.W.

Teaneck, New Jersey

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INTRODUCTION

SCIENCE, like the arts and crafts, has her amateurs, and some have become famous. What else were Charles Darwin, the country gentleman; Robert Chambers, whose *Vestiges of Creation* played such havoc with the religious beliefs of his day; Gregor Mendel, the priest and botanist; and Lord Cavendish, eccentric heir to an enormous fortune who lived on mutton and found out the composition of water? Lord Rayleigh, the discoverer of argon, was another, though he may have lost his amateur standing because he served for five years as Professor of Experimental Physics at the University of Cambridge.

Even princes and kings have not disdained to be amateurs of science or mechanics; witness Charles II, founder of the Royal Society of London, at work in his "chymical" laboratory; Philip, Duke of Orleans and brother of the Grand Monarch, amusing himself with "curious experiments"; and Louis XVI, the royal locksmith of France.

The amateur scientist has flourished in England particularly, where the clergy have done far more than their just share. Did not Henry Adams write, in his *Education*, that he found every curate there dabbling in geology? Joseph Priestley, who occupied himself with the chemistry of gases, was of the cloth and so were James Bradley, first to observe the aberration of light and the nutation of the earth's axis; John Ray, author of a standard work on systematic botany; John Flamsteed, the first Astronomer Royal; George Berkeley, renowned philosopher and valiant defender of tar water as a healing agent; Stephen Hales, first to determine the blood pressure; Gilbert White, famous for his *Natural History of Selbourne;* J. G. Wood, author of a two-volume natural history that was celebrated in its day; John Edwards, who developed an alloy with which to coat the mirrors of

reflecting telescopes; and James Little, who discovered one that he thought even better in respect to whiteness, luster, and freedom from tarnish.[13]

Not the least notable in this galaxy of clergymen-scientists was Jeremiah Horrocks, a young English curate who was inspired with an extraordinary zeal for the study of the heavens and, as the American astronomer Harold Jacoby so sympathetically wrote, thus united in one person the two most poorly paid professions in the world. Armed with a little telescope and defying a prediction of the mighty Johannes Kepler, Horrocks calculated that a transit of Venus would occur on November 4, 1639, and was not long in discovering that the eventful date would fall on a Sunday. But he was unable to predict the exact moment of the passage. What to do? Torn between duty and the desire to secure an observation he was almost beside himself until, allegiance to his church finally prevailing, he decided to spend at his telescope only the hours between services. He had his reward after all. Rushing home in the afternoon, he was just in time to see the round, black, planetary dot making its way across the sun's disk—the first transit of Venus ever to be observed. Before his death at the age of twenty-two this amazing young man had considerably advanced lunar theory, suggested that perturbations in the moon's orbit are referable to the sun, made observations on the tides, and investigated irregularities in the motion of Jupiter and Saturn.[5]

In the United States, too, science is eagerly cultivated as a hobby and chemistry, zoology, physics, geology, archeology, botany, and mineralogy all have their following.[18] Microscopy is a favorite subject, here as in England, not only for itself alone but because it is an invaluable aid to other hobbies such as botany and zoology. And certainly it has its points. An English enthusiast was once heard to remark that he could bring home in his waistcoat pocket an ocular or an objective for his microscope and his wife never a penny the wiser. Presumably an attempt to smuggle into the house a new camera or set of golf clubs, say, would have led to instant discovery and a painful accounting with the Little Woman.

There are no amateur surgeons, or physicians either. Among the arts and sciences medicine stands alone in this respect, for it requires such a highly specialized training and deals with matters of such grave import that it cannot be pursued as a hobby. Those outside its ranks who have made imperishable contributions have not been amateurs in the commonly accepted meaning of the word: one who persistently follows an avocation in which he endeavors to perfect himself. They have belonged to one of three groups, each of which will be represented in the pages to follow. First, those who, like Wilhelm Roentgen, were professionally engaged in the ancillary sciences and from whom great deeds might therefore have been anticipated. Then, like Benjamin Franklin or Gregor Mendel, amateurs of sciences that now at least are more or less unrelated to medicine. And finally, simple natives or humble country folk who must be forever nameless. This third group is by far the most interesting, because nothing new could reasonably be expected of it; yet at the same time it is least accessible to the historian, its discoveries having come about one hardly knows how. Their origins are lost in the mists of time, for they were never recorded. How could they have been? Nor, for want of the necessary training, were these pioneers able to develop their findings. Digitalis and vaccination, for example, both had to be tested and improved by practitioners of medicine and it is impossible, therefore, to omit the physician from the story of these precious gifts to mankind. Indeed, he looms large. But in the background of the picture, vague and indistinct though they be, stand the real heroes.

The first attempts of primitive man to cure disease were directed against the evil spirits that were assumed to cause it; then, after charms and incantations had been shown powerless to heal, various plants and animal products were tried, but the influence of the early belief was still apparent in the disgusting remedies that were employed to drive out the unwelcome visitors. Even after the physician had appeared on the scene the poor, in their extremity, used everything conceivable in an effort to lift the burden of illness and pain; for the physician was a luxury available to the rich alone. When one plan failed miserably another

was tried and another, and if these turned out to be inactive or harmful recourse was had to some animal product like owl broth, or the bile of a snail; and when this, too, proved inadequate to the task in hand a fried mouse was hopefully substituted. A beetle in a bottle, a toad in a linen bag, and anything else that seemed promising all had a fair hearing.

Slowly the picture came into focus as it grew increasingly clear that some plants, like the poppy, have the power to relieve pain; that some, like the foxglove, have other virtues; and that some are wholly impotent in the face of disease, if not actually poisonous. But the method of trial and error is long, generalizations were made too freely by those untrained in the gathering and sifting of facts, mistakes were inevitable, and disappointment or disaster was only too often the sole reward. A pertinent example of unwarranted inference has been given by J. C. Bateson.[1] An upholsterer, delirious from typhus fever, drank from a pail of pickled cabbage and recovered, whereupon cabbage juice was immediately proclaimed a sovereign remedy for this disease. But when the next patient died under the treatment the dictum was modified and cabbage juice declared beneficial only when the patient was an upholsterer.

Supplemented by chance observations, the weary process of experiment and elimination went on. Not by deliberate choice but from stark necessity. Not for any intellectual satisfaction derived from the search, as with the true amateur scientist, but because comfort and even life itself hung in the balance. And to these humble folk, casting about blindly in their distress, we owe such precious drugs as quinine, morphine, and digitalis.

Other remedies, too, some hardly less valuable than these, sprang from their bitter need.[8] Thus leaves from the coca, the "divine plant of the Incas," were used by South American natives before the Spanish invasion to ward off hunger and fatigue in exhausting toil or on long journeys, and the anesthetic properties of the drug appear to have been known to them. There was a custom among the Peruvians of opening old graves for the purpose of recovering sacred relics. As a result of inhaling effluvia or the impalpable dust into which the bodies fell after ex-

posure to air, the excavators often suffered from sore throat, until it was found that they could protect themselves by chewing coca leaves. The notice of European travelers was naturally drawn to this custom and eventually the active principle of the plant, cocaine, was isolated.

The diuretic properties of squill and the tonic effects of iron salts were known to the lay people of Greece five centuries before Christ; while ipecac, which induces sweating and, in large doses, vomiting, was familiar years ago to the natives of Brazil. Hottentots taught the colonists of South Africa the use of buchu leaves, long employed as a diuretic and for chronic inflammations of the urinary tract. Nor were the narcotic and sedative effects of *Passiflora incarnata*, the maypop, or passion flower, discovered by practitioners of medicine.

Curare, first used by South American natives as an arrow poison, was found by scientific investigators to act by paralyzing the motor end plates of nerves. Thereupon it became a valuable agent in physiological experimentation and was soon being administered at the bedside to relax muscular spasm of all sorts, most recently in connection with general anesthesia. Another arrow poison, familiar to the ancient Chinese, became the useful drug aconite, and still another, this one from Africa, is now employed by the physician as a powerful heart tonic: strophanthus.

Cod-liver oil was well known to the laity of northern Europe in remote times and given for various diseases, among them tuberculosis, or "white lights" as this was called in Scotland. The remedy was not often prescribed by physicians, however, until it was revived in 1841 by Dr. John Hughes Bennett, of Edinburgh,[9] and administered as a general nutritive in tuberculosis. One reason for the long delay was its disagreeable flavor, though one can acquire a taste for it. Children did, before chemistry relieved them of the necessity, and a friend of the writer who took it daily in mature years said that it tasted like caviar and was much less expensive besides.

As for preventive medicine, Moses has been called the greatest sanitarian of all time. Racial experience alone taught Israel the value of cleanliness, the necessity for isolation of the sick,

and the danger of contaminated water. The flesh of swine may have been excluded from the diet in order to prevent trichinosis, a dangerous disease that results from eating undercooked pork harboring the cysts of a parasitic worm, *Trichinella spiralis*, that infests the hog, the rat, and careless or ignorant people.

The suggestion has been made that the disease suffered by the Philistines when "the hand of the Lord was against the city with a very heavy destruction" was bubonic plague, and that the association of this disorder with rats (mice, the Bible has it) was recognized even in those early days. However this may be, the Chinese observed centuries ago an association between the death of rats in a house and the appearance of plague a few days afterward in the family living there. Yet in the Middle Ages the plague, then called the Black Death because of the dark, hemorrhagic areas in the skin, was ascribed in Europe to the poisoning of wells by lepers or Jews. The great medieval surgeon, Guy de Chauliac, on the other hand, referred it to the conjunction of three planets, Saturn, Jupiter, and Mars, in the sign of Aquarius.[14]

The Great Plague, which destroyed one fifth of the population of London during the summer of 1665, was thought to be spread by dogs and accordingly these were killed in great numbers. But the rats, later called by Charles Lamb in one of his famous letters the most despised and contemptible parts of God's earth—the rats, real carriers of the disease, went scot free. They were destroyed in the following year by the Great Fire of London, which put an end to the plague there.

Early in the twentieth century the Western world caught up at last with the ancient Chinese and Hebrews, when it was discovered that the plague is primarily a disease of rodents, and of rats in particular, and that it is conveyed by the bite of fleas. When the rat host dies the insects leave it, bearing the bacillus, and their second choice is man.

On the whole it is fair to say that medicine has often done no more than put the seal of its approval on folk beliefs. Benjamin Rush, one of the great figures in American medicine, was right

in telling his pupils that they could learn many useful methods of treatment from quacks and old women.

Surgery, too, is indebted to those outside its circle. Jacques de Beaulieu (1651–1714), a simple French laborer who became a Franciscan monk under the name Frère Jacques, did much to develop the operation of lithotomy, in which the bladder is opened for removal of a stone.[3]

According to Surgeon-Major William Curran [4] the drainage tube, so useful to surgeons for leading discharges out of a wound, is the invention of an army officer. Captain Creighton, wounded in battle at Aird's Moss, Scotland, about 1730, said that his surgeon had neglected to tie a string to the plug of green cloth that had been packed into the wound to keep it from healing over at the top. The plug slipped into the captain's body where it lay for over seven months, causing him great pain while at the same time it prevented the wound from healing. Accordingly he had some tubes made of a material unmentioned, through which the secretions could find their way out, and cut them shorter by degrees as he imagined the wound was healing from the bottom; when finally they became too short he replaced them with a larger one that was long enough. It was removed daily after the wound had been dressed with brandy and one morning, when it was taken out as usual, the plug followed and he knew that he would soon be well. This appears to have been the ancestor of the rubber drainage tube, popularized by Joseph Baron Lister, father of modern surgery. It had been introduced a few years before, rubber being by that time available, and Dr. Douglas Guthrie says that Lister employed it for the first time to drain an abscess under the arm. The patient was Queen Victoria.

The intravenous injection of drugs was first carried out by that consummate architect, Sir Christopher Wren, whose experiments were thus described by Thomas Sprat in 1667.

He was the first Author of the Noble *Anatomical Experiment* of *Injecting Liquors into the Veins of Animals.* An *Experiment* now vulgarly known; but long since exhibited to the Meetings at *Oxford,*

and thence carried by some *Germans*, and publish'd abroad. By this *Operation* divers Creatures were immediately purg'd, vomited, intoxicated, kill'd, or reviv'd, according to the quality of the Liquor injected: Hence arose many new *Experiments*, and chiefly that of *Transfusing Blood*, which the *Society* has prosecuted in sundry Instances, that will probably end in extraordinary Success.

Sprat was right in his belief that blood transfusion would end in extraordinary success, but wrong in calling it a new experiment. The earliest recorded account comes from Italy, where it was described in 1628. In France a young man with a high fever was transfused with blood from a lamb and by some miracle escaped death, but other transfusions performed during the next few years in France and in England were so often followed by disaster that the procedure was all but abandoned. It was given up entirely in 1875, after it had been proved that the blood of one species cannot safely be introduced into the veins of an individual from another species.

But even when human blood was employed it sometimes caused serious reactions, or even death. This was explained early in the present century when it was shown that human blood can be classified into four main groups. To avoid danger it is necessary to use blood of the group to which the patient himself belongs, and just recently it has been found that even some subgroups have to be compatible.

Yes, medicine has profited by contributions from those outside its own domain. But let no physician feel humiliated by this fact. Medicine has been called the most conservative of the professions, and it is right that it should be. Nothing is easier than to urge impatiently upon its practitioners a trial of this or that possible remedy, but after all theirs is the final responsibility. Before administering anything they must know that it will do good, or at least no harm, to those entrusted with such implicit faith to their care.

Moreover, medicine has not taken all and returned nothing. On the contrary, she has given generously of her sons to the arts, the sciences, and politics in its more dignified sense. To

etching, Sir Francis Seymour Haden, more renowned as artist than as surgeon. To music, Alexander P. Borodin, Russian composer. To literature, Sir Thomas Browne, best known for his *Religio Medici* and his *Urne-Buriall;* Oliver Goldsmith, "who wrote like an angel"; Robert Bridges, a Poet Laureate of England; Friedrich Schiller, German dramatist, poet, and philosopher; Tobias G. Smollett and Eugène Sue, English and French novelists respectively; Anton Chekhov, Russian dramatist and story writer; S. Weir Mitchell, equally distinguished as neurologist and novelist; François Rabelais, A. Conan Doyle, Oliver Wendell Holmes, and W. Somerset Maugham, none of whom require introduction to modern readers and, greatest of all, John Keats.

To politics, Sun Yat-sen, father of the Chinese Republic; and Georges Clemenceau, French statesman of World War I.

To science, Elisha K. Kane, naturalist and explorer; Thomas H. Huxley, staunch ally of Darwin; and Julius R. Mayer, German physicist and propounder of the law of the conservation of energy.

From time to time a layman has been given unmerited praise. Captain James Cook, who has often received the credit, did not discover the protective virtue of fruit juices. Their value was already known toward the middle of the sixteenth century and Sir Richard Hawkins, an English sea captain, was well aware of it in 1593. But the earlier experience was overlooked or forgotten and scurvy continued to exact a heavy toll among those that went down to the sea in ships, that did business in great waters. In 1535 the sailors of Jacques Cartier's expedition into Canada were ravaged by a violent form of the disease, to them a mysterious and unknown malady. The Indians were familiar with it, however, and taught the commander how to cure it with an infusion of bark and leaves from the hemlock spruce.[3, 7] Nor was scurvy unknown to the natives of Alaska, who employed green fir boughs as a remedy. Since the importance of fresh fruits and vegetables was recognized by Kramer, an Austrian army surgeon, in 1720; emphasized in 1739 by John Huxham, a phy-

sician of Devonshire; and demonstrated anew in 1753 by James Lind, a Scottish naval surgeon, Captain Cook did but popularize something that had long been known. His celebrated voyage, in which he lost only one man from scurvy out of 118 during a three-year trip, was not begun until 1772.

A second example of unearned praise is the soldier who was said by Oliver Wendell Holmes to have taught physicians how to cure gout: gout, which has tormented man from time immemorial and was described as follows, it has been said, by Dr. Morris Longstreth, of Philadelphia: [12] "Screw up the vise as tightly as possible, you have rheumatism; give it another turn, and that is gout." Actually it was Alexander of Tralles, a Byzantine physician of the sixth century who practiced his art in Rome, that taught the use of colchicum. He attributed its favorable effect to a purgative action, and it is interesting to note that this drug is still the chosen remedy today. The only difference is that instead of fluid preparations, like the wine of colchicum, which are sometimes adulterated and always uncertain, the crystalline active principle, colchicine, is prescribed. It is continued until nausea and vomiting or diarrhea set in, for rarely do the joint symptoms subside until after the first loose movement.[2]

It is difficult to know what soldier Holmes had in mind. Monsieur Husson, perhaps, a French army officer who introduced colchicum into France in 1785 as one ingredient of a secret mixture called *eau medicinale;* but this was recommended for all sorts of diseases, not specifically for gout.[15]

Finally, it has been said that Johannes Kepler, the astronomer, was the first to count the pulse or at least to have left a record of doing so, and that this took place in the year 1600. The greatest surprise has been expressed that among all the physicians who sat beside patients with a finger on that little artery in the wrist, none ever thought to count its pulsations.[8] This would be curious indeed if it were so. The fact is, however, that Herophilus, a physician of the Alexandrian school who lived about 300 B.C., counted the pulse rate with a water clock, or clepsydra, which measured time by the graduated flow of water through a small hole.[3]

II

THE BLOOD PRESSURE

The discovery of the blood pressure was more important than that of the circulation, wrote Johannes Müller, thus ranking the work of a comparatively unknown English clergyman with the labors of the immortal William Harvey.

The pioneer so honored by the great master of physiology was the Rev. Doctor Stephen Hales, who made the first quantitative investigation on the mechanics of the circulation by determining the height to which the blood rose in a vertical glass tube connected with an artery in dogs, and later in horses and other animals.

Hales was born at Bekesbourne, Kent, on an unknown day in September, 1677, the fifth or sixth son of Thomas Hales by Mary, daughter of Richard Wood, of Hertfordshire. Nothing is known of his boyhood, and he does not appear in medical history until, at the age of nineteen, he entered Corpus Christi College, Cambridge, as a pensioner, or student able to pay for his quarters. Here the consuming interest in science that governed his whole after life became at once apparent. Together with William Stukeley, later a celebrated antiquary, he roamed the fields of Cambridgeshire in search of plants and here, too, he worked at chemistry in the "elaboratory" at Trinity College, repeating many of Robert Boyle's experiments and learning in this way the value of the experimental method. Well grounded in Newtonian physics and in the astronomy of his day, he constructed an apparatus to show the motion of the heavenly bodies, similar to that afterward called an orrery after the fourth Earl of Orrery.[5, 7]

But the study of fossils and the dissection of animals claimed a large part of his attention, and he gave early evidence of his

extraordinary ingenuity by devising a method to obtain a cast of the lungs. Having removed these organs from a dog, he passed hot air through them by way of the trachea until they were perfectly dry in their inflated condition and then poured in lead, only just at its melting point in order that the bronchial tubes might not be destroyed. Finally the lungs were placed in water, where they were allowed to remain until their tissues had fallen away by maceration. The reward of all this patience and ingenuity was a perfect cast in lead of the bronchial tree, down to its very finest twigs.[11]

So scientific was his whole attitude toward life that it was said of him in after years: "he could look even upon wicked men and those who did him unkind offices without any emotion of particular indignation; not from want of discernment, but because he considered them only like those experiments which, upon trial, he found could never be applied to any useful purpose, and which he therefore calmly and dispassionately laid aside." [1]

After having received the degree of Bachelor of Arts, in 1702, Hales was admitted to a fellowship and took his Master of Arts in the year following, and his Bachelor of Divinity in 1711; and although he had pursued all his studies at Cambridge the University of Oxford, in 1733, conferred on him the degree of Doctor of Divinity.

In about 1709 he was appointed perpetual curate of Teddington, Middlesex. The year of his marriage to Mary, daughter and heiress of Doctor Richard Newce, rector of Hailsham, is uncertain but thought to have been about 1719.[8] She died without issue in 1721, and Hales never remarried. Because Mary's disposition was so angelic that he despaired of ever finding her like again? Or because, as has been remarked, a second marriage represents the triumph of optimism over experience? Who can say?

At Strawberry Hill, not far from the Teddington parsonage, stood the "little Gothic castle" of Horace Walpole, who called Hales "a poor, good, primitive creature"—a description vastly more revealing of the celebrated dilettante than of his neighbor. Alexander Pope, who lived near by, and could be venomous

enough if he chose, wrote that Hales was not more estimable for his discoveries as a natural philosopher than for his exemplary life as a parish priest. On one occasion the "wasp of Twickenham" was heard to say: "I shall be very glad to see Doctor Hales; he is so worthy and good a man."[8] A third famous neighbor was Frederick, Prince of Wales, and father of George III to be, who often used to visit Hales from the palace at Kew to watch him at his "curious researches."

His love for science, his "darling amusement," never caused him to neglect his pastoral duties and his little church, St. Mary's-in-the-Meadows, owed much to his unremitting care. He prevailed upon the lord of the manor to enlarge the churchyard, and caused a large bell to be hung in the tower "to be heard at a much greater distance, not only for the benefit of the serious and well disposed, but also as a constant memento to the careless, the negligent, and the profane. . . ."[5] Under his supervision the water supply of the parish was greatly improved, and characteristically Hales recorded that the outflow was such as to fill two quart vessels in "3 swings of a pendulum, beating seconds, which pendulum was 39 + 2/10 inches long from the suspending nail to the middle of the plumbet or bob."[5]

He was an ardent foe of intemperance, though by no means a prohibitionist, for he advocated the drinking of wine and as a Trustee of the Colony of Georgia approved the shipment of strong beer there, and the allowance of one quart daily for each of those embarking on the trip.[15] But in the early part of the eighteenth century the introduction of gin had given a new and a strong impetus to intemperance, and the gin shops of London were inviting passers-by to get drunk for a penny and dead drunk for twopence. Against this growing social evil Hales launched a vigorous campaign when, in 1734, he published his anonymous pamphlet: *A Friendly Admonition to the Drinkers of Brandy and Other Distilled Spirituous Liquors.* Two years later he was associated with a number of physicians in the preparation of another temperance tract, and at about the same time Hogarth published his print, "Gin Lane," at such a low price that it would be available to all.[5] Forced into action, Parlia-

ment restricted the sale of spirituous liquors, and the results of the campaign afforded Hales the utmost satisfaction; he wrote in a letter that it had made him happier than if he had prolonged the lives of a hundred million people.

True to his religious convictions, he made his female parishioners do penance for irregular conduct, though one editorial commentator [10] roguishly remarked that Peg Woffington, who was of their number, was probably not subjected to his discipline. The writer did not add, however, that the great Irish actress was about forty-three years old and in poor health when she retired to Teddington in 1757 to pass the rest of her days in good works such as the building and endowing of an almshouse. Hence Peg may not have required the clerical chastisement.

Though it has been said that his church was soon too small to hold all those who came to hear him preach, and that he had to build a new aisle, it has been intimated that his theology was ponderous and that his sermons were heavy. One that has come down to us because it was published as an anniversary sermon delivered before the Royal College of Physicians was said to have been so full of curious anatomical and physiological allusions that it was far more like a lecture on natural history than a sermon. Another, preached before his brother Trustees of the Colony of Georgia at St. Bride's, London, was described as dull.[13]

In short, as has been remarked, the name of the Rev. Stephen Hales does not figure very largely in the ecclesiastical literature of his day, and the student of church history in the eighteenth century will look in vain for the perpetual curate of Teddington.[16]

Certainly Hales was less fitted to theology than to science, where he succeeded so brilliantly, and surprise has been expressed more than once at his achievements. But most of his investigation was directed toward easing the lot of his fellow man, and it may be, too, that in his research he found confirmation of his faith. "We have good reason," he wrote,

to be diligent in making farther and farther researches; for tho' we can never hope to come to the bottom and first principles of things, yet in so inexhaustible a subject, where every smallest part of this wonderful fabrick is wrought in the most curious and beautiful manner, we need not doubt of having our enquiries rewarded with some further pleasing discovery; but if this should not be the reward of our diligence, we are however sure of entertaining our minds after the most agreeable manner, by seeing in everything, with surprising delight, such plain signatures of the wonderful hand of the divine Architect, as must necessarily dispose and carry our thoughts to an act of adoration, the best and noblest employment and entertainment of the mind.[5]

With amazing versatility he attacked one problem after another: deep sea sounding; the abatement of hurricanes by shooting bombs into the air; fermentation; earthquakes; distillation of fresh from salt water; the preservation of food and water in hot climates or on long sea voyages; the cleansing of rivers, harbors, and reservoirs; preventing the spread of fires; the measurement of high temperatures; the growth of bone; the origin of reflex movements, which he discovered to be in the spinal cord; the nature of gases; the bottling and storage of mineral waters; preserving biscuits and corn from maggots and weevils; electricity, and ventilation. He made chemical tests of a popular remedy for stone in the kidney or bladder that contained principally eggshells, snails, and soap, and finding that stones were not dissolved in a vial of the preparation even when it had been heated, reported that it was valueless, as indeed it was.[8] In using this "cure" Sir Robert Walpole is said to have consumed in the course of several years at least 180 pounds of soap and 1200 gallons of lime water; yet after his death three large stones were found in the bladder.[14] In respect to tar water, a highly vaunted remedy of the day, Hales exhibited a praiseworthy caution, confining his published remarks to a discussion of its chemistry and preparation, together with the hope that his investigations might be of use in skilled hands by adapting it "to different Cases and Constitutions. This is the proper Province of the Physician, which I am in no ways qualified to meddle in." [8]

The year 1741 witnessed one of those occurrences that are not rare in science.[8] An idea presented itself independently to three men: Samuel Sutton, proprietor of a London coffeehouse, who proposed to draw off the foul air aboard ships by means of the galley fire; Martin Triewald, military architect to the King of Sweden, who invented a machine for the same purpose; and Stephen Hales. The apparatus of Triewald was similar to that of Hales, which took the form of large bellows resembling those of a church organ and was at first operated by hand. Unlike Sutton's invention, these two met with almost instant recognition and were immediately successful in convict ships and vessels of the slave trade, reducing the mortality on those carrying African Negroes to the United States from some 25 per cent to 5 per cent or less.

In France, Louis XV was persuaded to introduce the ventilators into prisons where British soldiers were confined, and the reverend inventor was heard to say "merrily" that he hoped no one would inform against him for communicating with the enemy.

Ventilators of large size were turned by windmills. Such a one in Newgate Prison, which was connected by tubes with twenty-four wards, reduced the mortality by more than 50 per cent in the first four months after its installation, and in other British prisons and in the smallpox hospitals the results were equally gratifying.[5]

No project was too large for Hales, and none too small. A miniature copy of the ventilator was designed to whip cream by blowing air through it, as the following letter will show. Doctor Pyle, chaplain to George II, wrote to the Reverend Doctor Kerrich:

Dear Sir,—The only articles, of that sort, that I know of, are: That Dr. Hales hath actually published: what has been sometime talked of; a tube of tin, with a box, of the same, at the lower end of it (like a box for a great seal), that is full of very small holes. This engine, with the help of a pair of bellows, blows up cream into syllabub, with great expedition. This complex machine hath already procured the Dr. the blessing of the housekeeper of this Palace, and of all

such as she is, in the present generation (who know the time and labour required to whip this sort of geer *): and will cause his name to be had in reverence, by all housekeepers, in the generations that are yet for to come.[5]

Well, the ventilators have gone their way and disappeared from ship, jail, and kitchen to be replaced by more efficient measures, but their inventor still stands today as one of the pioneers in public health.

A second great accomplishment was his botanical work, less important from a practical standpoint but of the highest scientific interest nevertheless. In 1719 he reported before the Royal Society of London some experiments on the raising of sap in trees by the sun's warmth. His paper gained him the thanks of the Society, coupled with the request that he continue his investigations; and with this, wrote Collinson, which was like the charge given by Pharaoh's daughter to the mother of Moses that she take care of him, Hales complied with the greatest pleasure. The result was his *Vegetable Staticks*, published in 1727 and described by Sachs, the celebrated German botanist, as the most original and important contribution of the eighteenth century to botany. Further recognition came from John Ellis, prominent naturalist and governor of the Colony of Georgia, who named the newly discovered silver-bell tree of southeastern North America *Halesia* in honor of the amateur botanist.

Hales made the first scientific investigation of the sap in plants, measuring the transpiration of water from the leaves and its absorption by the roots, calculating the rate at which sap flowed along the stem and branches, and determining its pressure, which he found to be five times as high as the blood pressure in the horse. Observing that the movement was upward under all circumstances he argued against the theory then and long afterward current that the sap circulates, and attributed its elevation to transpiration and a force exerted by the roots. Of this work he wrote, in words that have been echoed by scientists the world over so many times since: "I have been careful in making, and faith-

* Scottish for food or liquor.

ful in relating, the results of these experiments; and wish I could be as happy in drawing the proper inferences from them." [5]

But it is for his determination of the blood pressure that Hales is best known, at least in the world of medicine. He began the work because of a desire to test "unsatisfactory conjectures": that the contraction of muscle is induced by its fibers being dilated, and hence shortened, by the force of the blood. These epoch-making experiments were described in *Hæmastaticks*, published in 1733; together with *Vegetable Staticks* it makes up his *Statical Essays*, which, translated into French, German, and Italian, brought him international renown. A Fellow of the Royal Society since 1718 and elected to its council in 1727, he received the Copley Medal in 1739, the highest honor that the Society could bestow; and in 1753 became one of the eight foreign members of the French Academy of Sciences in the place left vacant by the death of Sir Hans Sloane, successor to Sir Isaac Newton in the presidency of the Society.[8]

Finding little satisfaction in previous endeavors to determine the blood pressure, he made up his mind to experiment for himself:

Several ingenious Persons have, from time to time, attempted to make Estimates of the Force of the Blood in the Heart and Arteries, who have as widely differed from each other as they have from the Truth, for want of a sufficient Number of *Data* to argue from: Had Persons of their Abilities been more careful, in the first Place, to get what Insight they could into the Matter, as far as a regular Series of proper Experiments would have informed them, they would then doubtless have been furnished with more and more proper *Data* whereon to found their Calculations, which would have brought them much nearer to the Truth.[9]

Tying a glass tube, the first manometer, vertically into an artery or a vein of a living animal, he recorded the height to which the blood rose in it—a decisive step in cardiac physiology and the basis for all subsequent exact studies on the circulation. It seems curious that such a meticulous observer should not have dated his experiments, but apparently he did not. He wrote that

EXPERIMENT III
TUBE IN THE CAROTID ARTERY
A MODERN ARTIST'S CONCEPTION

the earliest ones had been carried out on dogs "about twenty-five years since," which would have been about 1708, and that some six years later he repeated the investigation on horses; altogether he employed twenty dogs, three horses, a sheep, and a doe. The first estimation on a horse is described in the following words:

In *December* I caused a mare to be tied down alive on her back; she was fourteen hands high, and about fourteen years of age, had a *Fistula* on her Withers, was neither very lean, nor yet lusty: Having laid open the left crural Artery [the great artery in the groin that supplies the leg, now called the femoral artery] about three inches from her belly, I inserted into it a brass Pipe, whose bore was one sixth of an inch in diameter; and to that, by means of another brass Pipe which was fitly adapted to it, I fixed a glass Tube, of nearly the same diameter, which was nine feet in Length; then untying the Ligature on the Artery, the blood rose in the Tube eight feet three inches perpendicular above the level of the left Ventricle. . . .

In a second experiment, in which the same tubing was employed, the gelding was "somewhat lustier than the mare, and much more lively." Hence the blood attained a height of nine feet and eight inches, rising and falling from one to three inches at each contraction of the ventricle as it had before.

But his Experiment III is the most interesting of all, for it shows so clearly the ingenuity of the man. The rigid joint between the brass and the glass tubing had caused him much inconvenience when the horses struggled, and he needed a flexible one. Rubber tubing he had never heard of, naturally enough, for rubber did not come into extensive commercial use until about the beginning of the nineteenth century,[17] so he made his pliable connection with the windpipe of a goose!

Hales presented many of his results in tabular form, which led to the publication of a note in a later edition of his *Statical Essays* that gives an interesting view of the general educational level at the time.[1]

Whereas some complain that they do not understand the signification of these short signs or characters which are here made use of in many of the calculations, and which are usual in algebra: this mark +

signifies "more," or "to be added to." Thus 6 ounces + 240 grains, is as much as to say 6 ounces more by or to be added to 240 grains. And this mark × or cross signifies "multiplied by"; the two short parallel lines signify "equal to"—thus 1820 × 4 = 7280 . . . is as much as to say 1820 multiplied by 4, equal to 7280. . . .

After he had finished his experiment Hales killed each of the horses by bleeding, since they were to have been destroyed in any case as unfit for further use, recording the pulse rate as the volume of circulating blood became smaller and smaller, and endeavored to compute the amount of blood that would circulate during life. A necropsy on one of them showed that "There might be about two quarts and three quarters of blood left in the large veins, which, with what was drawn out at the artery, makes five Wine gallons, which at 221 Cubick inches to the gallon, amounts to 1105 Cubick inches, or 42.2 pounds; which, at a low estimation, may be reckoned the amount of current blood in a horse; there is, doubtless, considerably more, but it is not easy to determine how much."

The blood pressure in man he put at about seven and a half feet, which is a little high,[4] modern authorities suggesting five or six feet as more nearly correct. Still, it is remarkable that with his crude apparatus he should have come as close as he did.

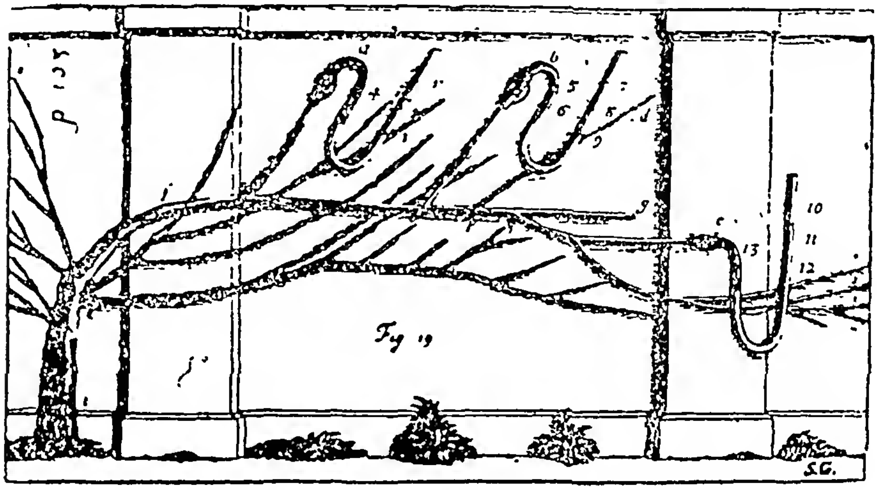
Since we think of pressures today in terms of weight, the distance that the blood ascended in his experiments means but little as it stands, except that in the first horse, say, the pressure was equal to the weight of a column of blood eight feet and three inches high. As the diameter of the tube was given, however, and the specific gravity of the blood is well known, it is a simple matter to compute the weight of such a blood column, and hence the pressure, which works out at about 3.75 pounds per square inch, or somewhere in the neighborhood of 2.5 pounds for man. Of course the blood pressure is never indicated in pounds per square inch, and the figure is given only that the reader may have some idea of the pounding taken by the larger arteries seventy times a minute and day after day. As this is but a rough estimate the distinction between end and lateral pressure may be ignored.

The direct method employed by Hales obviously could not be used in the human subject unless, perhaps, in a few selected cases, so it was necessary to find some way of measuring the blood pressure indirectly. This was finally achieved in 1855 by Vierordt,[16] who formulated the principle that an indirect determination can be made by ascertaining the counterpressure that will obliterate the pulsations in an artery. His apparatus, which employed weights, was complicated and clumsy, as were those advanced by most of his immediate followers, and four decades of trial, error, and partial success ensued until, in 1896, Riva-Rocci described the accurate and compact sphygmomanometer that still prevails.

Vierordt's principle is retained, but the blood pressure is balanced against the pressure of air in a long, flat rubber bag that is secured above the elbow and inflated with a hand bulb until the arterial flow has been shut off. Communicating with the bag there is a U-shaped tube containing mercury and so connected that the air pressure from the bag is applied to the top of the mercury column in the open end, forcing that in the closed arm of the tube to rise, and the difference in height of the two columns, read off at the proper moment, gives the blood pressure in millimeters. The U shape of the tube, of course, halves the necessary length of the mercury column. It remains only to add that the manometer is replaced in some models by a gauge resembling an aneroid barometer, but graduated to read in millimeters of mercury since this is the manner in which blood pressures are expressed today.

The invention of the mercury manometer is ordinarily credited to Poiseuille, a young French medical student, who in 1828 described in his graduation essay the substitution of such an instrument for the long, vertical tubes of Hales. But it is a fair question whether Stephen Hales himself may not have been the inventor, for he mentioned repeatedly a mercury gauge and actually showed several in a cut illustrating sap pressure. Yet it does not appear in his account of the work on blood pressure, either in words or in pictures, and an unsigned article in the *Medical Times* asks why he did not employ it, instead of his long, cum-

bersome tubes.[11] The only answer found is that Hales must have developed the use of the mercury manometer later, in the course of his experiments on sap.



Determination of Sap Pressure

In any case, mercury was utilized in physiological laboratories, where there was no restriction on the direct method, long before Riva-Rocci's instrument appeared, because mercury is about 13.5 times heavier than blood, so that a column of the metal will rise only a fraction of the distance that the blood itself would ascend in a vertical tube. And a good thing, too! At least from the practical standpoint, for otherwise the physician would have to carry with him on his rounds a slender glass tube somewhat over 13 feet long, or a mere 6 feet or so if he bent it into a U shape, and filled with some fluid having the specific gravity of blood, since in patients with hypertension the blood pressure might be sufficient to raise such a fluid almost to this height.

What is the normal blood pressure in the human subject? How long is a piece of string? The only answer is that thoroughly annoying one: It all depends. The blood pressure is affected in so many ways; by habit, by constitutional type, by race, and by many other factors. It is higher after eating and during exercise and emotional excitement, as Hales had noted, lower during sleep,

and so on; higher in large, broad-chested men than in those of slighter build, so that a pressure normal for Tarzan would be high for Caspar Milquetoast. But at any rate the common belief that it should equal the age plus 100 is erroneous, for the figure would be too high.

With all the qualifications given, and some others in addition, it may be said that the blood pressure rises slowly from about 40 at birth through 120 or so at seventeen to something like 140 at the age of sixty. These figures relate to men and to the maximal, or systolic, reading, taken at the height of the left ventricle's contraction, which is the blood pressure that everyone talks about. The minimal, or diastolic pressure, never mentioned at bridge or cocktail parties, though highly important for all that since it represents the constant load on the larger arteries, is determined at the end of the rest period, or diastole, when the heart is fully dilated; it should be a little more than half the systolic pressure, or 70, say, for a systolic pressure of 120. The pulse pressure is the difference between the two; in this case 50.

In women the systolic pressure runs 4 or 5 millimeters lower than in men until the change of life, when it rises rather abruptly and thenceforth continues to be somewhat above the male average; yet women, who do all the housework, bear and rear the children, and in general outlive men by several years on the average, seem to tolerate higher blood pressures. Indeed, it has been said facetiously that if she passes through the middle years safely a woman becomes virtually immortal.

In the obese the blood pressure is definitely higher than in the sparely built—7 to 8 millimeters or more; and as a high blood pressure may mean danger, in men at least, it is wise not to forget the famous pushing exercises of a few decades ago: pushing oneself away from the table three times a day. It has been estimated that for every 20 pounds of surplus weight the heart must pump blood through 12 miles of extra vessels, a tremendous additional burden.

Hales said that the blood pressure varies among different animals, and so it does, but the deviation is great only in widely separated species such as he could not have examined for lack of

the necessary delicate apparatus and special skill. The relatively large variations that he reported among mammals were no doubt due to factors beyond his control, as the following figures for systolic pressure from Bazett and from Best and Taylor, expressed in millimeters of mercury, will show.

Mouse	113
Rat	100
Rabbit	90–105
Cat	105–115
Dog	110–120
Horse	155
Canary	220
Robin	118
Frog	43
Turtle	44
Carp	43

Thus among mammals the differences, on the whole, are not wide, and there is little relation to size; the suggestion has been advanced, in fact, that the blood pressure in the elephant may be much the same as in the mouse. Furthermore, what increase there is with size appears to be due to height more than anything else; in other words, to the weight of a long column of blood, so that the giraffe, it has been explained, may very well have a higher blood pressure than the elephant.

Hales wrote that after he had completed his first experiments on the blood pressure he did not pursue the matter any further for a time, being "discouraged by the Disagreeableness of Anatomical Dissections." [16] Alexander Pope disapproved thoroughly of this work, despite his high esteem for the reverend investigator, but Hales was encouraged later to resume the inquiry "by Variety of such Experiments as I conjectured would give some Light into the Matter." [16]

He was right in so doing, for what was the pain of his twenty-five animals compared with the incalculable benefits to the human race that have followed from his work? Preliminary experiments cannot by any possibility be done on the human patient,

yet they must be carried out somehow unless all progress in medicine is to stop. Fortunately for both animals and investigators, who certainly are not the callous villains pictured with such relish by the antivivisectionists, experimental work can now be conducted without pain to either. Shall mankind continue to suffer and die unnecessarily because of the emotionalism of a few sentimentalists, who do not even seem to know that the lower animals benefit in common with man as experimental medicine advances?

The question with which Hales began his experiments on the circulation was finally answered. Estimating the decrease in its force as the blood made its way through the capillaries, he found that the pressure lost at any one point is wholly inadequate to account for muscular activity. A more vigorous energy, regulated by the nerves, seemed to him requisite. "But whether it be confined in canals within the nerves, or acts along their surfaces like electrical powers, is not easy to determine."[4] Unlike his contemporaries, he was not satisfied to invoke the "animal spirits," a favorite explanation in his day for much that goes on in the body, and since then identified as electrical impulses. Everything must be weighed, measured, and analyzed if this were at all possible, or at least explained by some agent already known. ". . . in natural Philosophy we cannot depend on any mere Speculations of the Mind; we can only, with the Mathematicians, reason with any tolerable Certainty from proper *Data*, such as arise from the united Testimony of many good and credible Experiments."

But his studies on the circulation went far beyond a determination of the blood pressure. He measured the capacity of the heart, the diameter of the blood vessels and the strength of their walls, the rate at which the blood flows, and showed how the elasticity of the arteries carries it along at an almost even speed after the end of the systole, so that it does not advance in spurts but "in the same manner as the spouting water of some fire-engines is contrived to flow with a more even velocity, notwithstanding the alternate . . . rising and falling . . . force; . . ."[5]

He found, too, that heat, cold, and various other agents will either dilate or constrict the smaller blood vessels. Brandy, for example, contracted those of the intestine and his practical mind immediately applied this observation to a matter in which he had always been deeply concerned.

'Tis probable, that such things as constringe the vessels in any degree, do also proportionably increase the force of the arterial blood, and thereby invigorate the animal. . . .

But those who much accustom themselves to drink strong spirituous liquors, do thereby destroy the tone of the fibres of their vessels, by having them, thus frequently, suddenly contracted, and so soon relaxed again; which make them like the horse-leech, be ever longing after and thirsting for more and more, thereby to regain the *tensity of their too relaxed fibres.*

Hales estimated the capacity of the heart by filling a number of such organs with melted beeswax, then cutting the tissue away and immersing the casts in water to see how much they displaced. The inside area of the cardiac walls was determined by covering the casts with bits of paper, "aptly cut," and measuring the total area of these on paper ruled in quarter-inch squares. With capacity and area known, as well as the blood pressure, the heart rate, the diameter of the aortic orifice, and that of the aorta itself, he calculated for various species the total pressure sustained by the heart's wall at the beginning of each contraction, setting it at a little over 113 pounds for the horse and about 51 for man. But the capacity of the heart cannot be determined with melted wax, or in any other way with reasonable accuracy, so all these computations were more or less incorrect.[9] Nevertheless, Hales took the first great step after Harvey, who had shown that when the heart contracts the blood is driven from the right side of the heart through the lungs and, returning to the left side of the heart, pumped by the left ventricle into the general circulation. But Harvey said nothing about the pressure of the blood.

Hales alternated between animals and plants, experiments on one suggesting investigations on the other. His work on the blood pressure in dogs thus led to that on the pressure of sap,

while a chance observation that bubbles of air ascended with sap was responsible for his leaving the problem of the circulation to explore the chemistry of respiration.

But he never did find out what the lungs are for. He was inclined to think that their principal use was to cool the blood, heated by the friction of its corpuscles; but whereas others had been content to discuss the question in a vague way he must needs have calculated for him the precise amount by which its temperature is lowered. His mathematical collaborators, having been given the quantity of blood passing through the lungs per minute, the amount of air breathed during the same time, and the temperature of the inspired and expired air, calculated that in two minutes as much heat is lost through the lungs as would raise all the blood in the body about one tenth of a degree Fahrenheit; or, conversely, if a man held his breath for two minutes, "as Grano the trumpeter can," the temperature of his blood would be raised about one tenth of a degree.[9]

Since blood becomes redder when shaken in air, as it does also in passing through the lungs, Hales suggested that it might be shaken by their movements, though he was unable to see why this should be of any advantage. Yet clearly he was on the right track. "'Tis probable also, that the blood may in the lungs receive some other important influences from the air, which is in such great quantities inspired into them. It has long been the subject of enquiry to many, to find of what use it is in respiration, which tho' it may in some respects be known, yet it must be confessed that we are still much in the dark about it." [9]

Perhaps he was referring to the work of Lower, who more than sixty years before the publication of *Statical Essays* had clearly recognized that the blood is purified by absorbing from the air something that we now call oxygen. But whereas Hales knew at least a little about this great pioneer, whom he mentions by name, he had virtually no theoretical knowledge of science, having been concerned mainly with practical matters. He did realize, though, the vital importance of air as a whole, which he once described as "that genuine cordial of life," but he had no idea of the manner of its action. Small blame to him,

however, for the work of Lower, Mayow, and other pathfinders (see Chapter III) had been sadly neglected on all sides.

Hales invented also the method used in studying the growth of plants by marking stems and leaves at equal intervals, an innovation of special interest to medicine because it led to his work on the growth of bone. He showed that the long bones grow from their ends and not along the shaft, by making two small marks with a sharp-pointed instrument about half an inch apart on one of the bones in the leg of a half-grown chicken. Two months later, when it was killed, the marks were still half an inch apart though the bone had increased in length by an inch, chiefly at the upper end. This experiment, usually credited to John Hunter, was actually performed by Hales some years before Hunter was born.[5]

In his last experiment, at the age of seventy-nine, Stephen Hales returned from applied science, as represented in his ventilators, to comparative physiology, and after the lapse of forty years completed his work on respiration. He placed an equal number of small fish in each of two pails of water; in one the water was ventilated with air whereas in the other it was allowed to become stagnant. The fish in the former pail remained well, but those in the latter became ill and soon died. "Hence we see the Benefit of frequently replenishing the Water with fresh Air, which we find is necessary not only to preserve the Life of Land Animals, but also of Fish; as also the use of their Gills, to spread in thin Sheets fresh Supplies of Water; for which Purpose both Sides of their Gills are furrowed with many fine Furrows, thereby to enlarge their Surfaces." [5]

Despite his scientific interests Hales continued his clerical duties almost to the end, and in a trembling hand his signature appears on the parish register for the last time on November 4, 1760. He died on the following January 4, at the age of eighty-four, after a short illness the nature of which is not known. At his own wish he was buried under the tower of the church that he had served so long and loved so well, but his monument stands in Westminster Abbey.

Unnecessarily, perhaps. In St. Paul's lies Sir Christopher

Wren, its architect, and over a doorway are the words: *Si monumentum requiris, circumspice.* Yes! If you require a monument, look about, and you will find the Hales manometer in use today for the instruction of medical students in the first elements of hemodynamics.

III

RESPIRATION

We of today, who are so familiar with the course of the blood as it makes its way through the body, refreshing the cells and removing their waste products, find it difficult to understand why the purpose of breathing should have remained an insoluble problem for so many years. The reason is that its elucidation had to await the discovery of the circulation of the blood and, more necessary still, the development of chemistry.

For centuries it was widely believed that the liver is the seat of life, that the veins originate there, and that they are the only vessels carrying blood, since the arteries were always found empty after death. These were supposed to contain nothing but "vital spirits" or air, as the very word "artery" bears witness, coming as it does from two Greek words meaning to hold air.

This venerable and utterly mistaken opinion was modified by the Greek physician Galen, who practiced his art in Rome during the latter half of the second century, founded experimental physiology, and was, after Hippocrates, the most distinguished physician of antiquity. Galen proved that the arteries are filled with blood during life. He knew that this vital fluid is poured into the right side of the heart by the great veins, but thought that only a small quantity passes from the right ventricle into the lungs; most of it, he believed, enters the left ventricle through minute pores that he imagined were in the septum dividing this from its companion chamber on the right side of the heart.[5]

His erroneous conviction held sway until the middle of the sixteenth century. Then Michael Servetus, Spanish lawyer, physician, and theologian, denied that blood passes through the interventricular septum, insisting that it returns from the lungs

to the left side of the heart through the pulmonary veins, as, indeed, it does. Others supplemented this great discovery by explaining the function of the cardiac valves as best they could and describing a perpetual movement of blood through the heart, but the movement was still pictured as to and fro.

All this was changed by the genius of William Harvey. As a result of reflection, calculation, and experiment he was able to prove that the motion of the blood is not simply to and fro, but circular. He offered no reason, however, *why* the blood should circulate, confessing that he was not sure whether for the communication of heat or for some nutritional purpose.[5]

His book, *De motu cordis*, published in 1628, gave rise to a controversy that lasted for more than twenty-five years and drew in physicians, naturalists, philosophers, and everyone else who could lay claim to any knowledge of anatomy or physiology. Nor was the quarrel restricted to these alone. The general public entered the fray, declaring Harvey a crackbrain, and so bitter was the feeling against him that he lost much of his practice and even feared for his own safety. Such was the reward of him who had made the most important physiological discovery in all the history of medicine!

In the face of this widespread detraction and a diminishing practice Harvey maintained a dignified and admirable silence. He could afford to wait. His book was published when he was fifty years of age, and as he lived to be nearly eighty there was ample time for vindication. René Descartes was first among the illustrious to declare in his favor; then Jan de Wale, celebrated professor of anatomy at the University of Leyden, confirmed Harvey's view by new observations; and finally Plempius, of Louvain, for a time one of the most bitter opponents, succumbed to the truth and in 1652 went publicly over to the ranks of Harvey's followers.

Only one link in the chain of evidence was lacking. Harvey realized that there must be some sort of passage through which the blood could flow from the smallest arteries into the smallest veins to complete the circulation, but as he was not a microscopist he remained in the dark. The final discovery was made by one

who was skilled in the use of the microscope: Marcello Malpighi, born near Bologna in 1628, the year in which Harvey's book appeared. Until 1661, when the Italian histologist published his *De pulmonibus*, the lungs had been regarded as a sort of porous tissue, a sponge, within which the smallest branches of the pulmonary artery lost themselves to pour their blood into open spaces, where it was taken up by the tributaries of the pulmonary veins. The smallest branches of the windpipe, too, were thought to end in this porous tissue, inspired air mixing directly with the blood.[13]

But in the lungs of frogs, tortoises, and dogs Malpighi spied air vesicles continuous with the smallest branches of the trachea, and discovered that the air in these little chambers never comes into actual contact with the blood at all. This, he found, is contained within minute vessels whose extremely thin walls separate blood and air—the capillaries, so called because they are slender as a hair. "Harvey made their existence a logical necessity; Malpighi made it a histological certainty," as has been so well said by Fraser Harris. As is now known, the walls of the capillaries and small air chambers are so thin that the life-giving oxygen can readily pass through them into the blood.

Now the path of the circulating blood was completely understood. Now it was known that this is driven from the left ventricle through the arteries to the entire organism except the lungs, that it passes from arteries to veins by way of the capillaries and returns through the veins to the right auricle; that it flows thence into the right ventricle, from there through the lungs into the left auricle, and finally back to the left ventricle again.

But all this did little to explain the function of the lungs. The ancients believed that the air passing into them serves merely to cool the heart, source of bodily heat, and keep the inflammable lungs from catching fire. Later it was thought that the blood is warmed by the friction of its corpuscles rather than by the heart, but whatever the origin of its heat the idea that the function of breathing is only to cool it persisted until the middle of the seventeenth century.

The true purpose of respiration was explained in part by four young scientists of Oxford, only one of whom was a physician.

Robert Boyle, seventh son and fourteenth child of the first Earl of Cork, was born at Lismore, Waterford, on January 25, 1626. Possessed of ample means, he devoted his wealth and talents to the pursuit of science.

Wishing to learn why breathing is so necessary to all animals that have lungs, he put a lark into a glass vessel from which he gradually removed most of the air with an air pump. The bird died in violent convulsions after less than ten minutes, and under the same conditions a sparrow seemed to be dead at the end of seven minutes, but revived when air was let into the vessel. Upon repetition of the experiment the little creature died in convulsions after the lapse of five minutes, and a mouse similarly. These were crucial experiments, for they showed that in the partial absence of air not only animal life but the flame of a candle is extinguished. Air, he concluded, is essential to both life and combustion.[16]

Boyle's assistant, Robert Hooke, was a singularly able man; a highly ingenious experimentalist and an accurate observer. He was born at Freshwater, on the Isle of Wight, on July 18, 1635, and at the age of twenty-five received the degree of M.A. from Oxford University, where he had already become conspicuous by reason of his many mechanical inventions.[16] Small and deformed, with unkempt hair falling like a mane over an ashen countenance, he grew more shrunken and more crooked as the years went by. Crabbed, jealous, and vain, hated and despised by most members of the Royal Society, he was so miserly as to deny himself all but the barest necessities of life; yet after his death several thousand pounds were discovered in an old iron chest, the rusty key of which had lain unused for over thirty years. Toward the end of his life his temper had become really intolerable but behind those unfriendly eyes and disheveled locks, says Victor Robinson in his *Story of Medicine*, burned the fire of genius. His inventions in air pumps, watches, microscopes, and meteorological instruments were almost without number, and

turn where we may in science we are sure to discover the footsteps of Robert Hooke. He could experiment with soap bubbles or speculate on the motion of the heavenly bodies with equal facility, and was the only man of his century that listened to the sounds of the heart and lungs. When London was rising from the ashes of her Great Fire he was in constant demand as surveyor and builder, an occupation from which he reaped a small fortune.

On October 24, 1667, Hooke gave an account before the Royal Society, whose Curator of Experiments he was, of some investigations in which he had kept a dog alive for an hour or more by blowing air through its lungs with a pair of bellows, alternately distending them and allowing them to subside. As some prominent physicians had declared their motion essential to life because it promoted circulation of the blood, and had said that an animal would suffocate immediately if its lungs stopped moving, Hooke made the following additional experiment.

A second pair of bellows connected to the first was kept always full and blowing air into the lungs. Thus these organs were constantly inflated and motionless, the air escaping slowly through minute holes pricked in their surfaces with the point of a knife, instead of more suddenly as it would in expiration. During this experiment the dog lay quiet, and its heart continued to beat regularly. When the blast of air was discontinued, however, and the lungs were allowed to collapse, the animal was seized with convulsive fits and appeared to be dying, but recovered as soon as the lungs were filled again with a constant stream of fresh air. It was abundantly clear that the motion of the lungs contributed nothing to the dog's life, since he survived whether they moved or not. It was lack of air that caused death, as Boyle had shown.[16]

Though these experiments have been called the first of their kind they really were not. Andreas Vesalius, the foremost anatomist of all time, had proved in 1543 that an animal whose chest had been opened, as had those of the dogs in Hooke's demonstration, and whose lungs were collapsed in consequence, can be kept alive by artificial respiration.[1]

Hooke's work showed once more that an adequate supply of

air is necessary for life, but did not explain why. This side of the problem was solved by Richard Lower and John Mayow.

Richard Lower, scion of an old family with substantial possessions, and the only physician in the Oxford group, was born near Bodmin, Cornwall, in 1631. He took his M.A. degree at Oxford in June, 1653, the year in which Oliver Cromwell was proclaimed Lord Protector of England, and the degrees of Bachelor and Doctor of Medicine in 1665, the year of the Great Plague in London. He missed the Great Fire in September, 1666, because he was in Cornwall, courting Miss Elizabeth Billings, no doubt, for they were married in the following November.

Together with his contemporaries Lower had been taught that the heart generates heat, that this is imparted to the blood stream, and that the purpose of respiration is to cool the blood. But he was a disrespectful and rebellious pupil, for he did not believe what his teachers said. It was well known at the time that arterial blood is bright scarlet in color, and venous blood darker and purplish, though the difference was ascribed to some sort of combustion taking place in the heart. Lower regarded this dissimilarity as a matter of the greatest importance, and resolved to investigate it thoroughly. Having noted that the surface of a blood clot becomes bright red when exposed to air, he asked himself whether the same change occurs in the blood as it passes through the lungs, and by repeating Hooke's experiment convinced himself that it does. He found, further, that when he discontinued the artificial respiration the blood in the lungs became dark and venous in color, but scarlet once more when the respiration was resumed. He then passed venous blood through the lungs, and saw that as long as these were kept full of air it flowed out of them scarlet in hue. If no fresh air were blown into the lungs, or if they were kept distended with the same air, the perfused blood emerged still venous. He concluded that the color change is effected in the lungs, and effected by air. But as the atmosphere was not then known to be a mixture of gases he had no reason to ask which one among its several constituents is responsible for this alteration.

His epoch-making discovery was neglected, and in some quarters even opposed.[9, 16]

Lower was the first to transfuse blood from one animal to another; probably, it has been surmised, at the suggestion of Sir Christopher Wren. The experiment, repeated by Dr. Edmund King before the Royal Society at Gresham College, Oxford, was described by Samuel Pepys in his *Diary*.

On Novemer 14, 1666, this enthusiast for anything that was new attended "an exceeding pretty supper," and was told by Dr. Croone

> that, at the meeting at Gresham College to-night, which, it seems, they now have every Wednesday again, there was a pretty experiment of the blood of one dogg let out until he died, into the body of another on one side, while all his own run out on the other side. The first died upon the place, and the other very well, and likely to do well. This did give occasion to many pretty wishes, as of the blood of a Quaker to be let into an Archbishop, and such like; but, as Dr. Croone says, may, if it takes, be of mighty use to man's health, for the amending of bad blood by borrowing from a better body.

At noon, on November 16, Pepys met Mr. Hooke "and he tells me the dog which was filled with another dog's blood, at the College the other day, is very well, and like to be so as ever, and doubts not its being found of great use to men; and so do Dr. Whistler, who dined with us at the taverne."

Twelve days later ". . . Mr. Carteret and I to Gresham College . . . and here they had good discourse how this late experiment of the dog, which is in perfect good health, may be improved for good uses to men, and other pretty things, and then broke up."

November 21, 1667, brought the following entry:

> From this we fell to other discourse, and very good; among the rest they discourse of a man that is a little frantic, that hath been a kind of minister, Dr. Wilkins saying that he hath read for him in his church, that is poor and a debauched man, that the College have hired for 20*s*. to have some of the blood of a sheep let into his body; and it is to be done on Saturday next. They purpose to let in about twelve ounces; which, they compute, is what will be let in in a min-

ute's time by a watch. They differ in the opinion they have of the effects of it; some think it may have a good effect upon him as a frantic man by cooling his blood, others that it will not have any effect at all. But the man is a healthy man, and by this means will be able to give an account what alteration, if any, he do find in himself, and so may be usefull.

A footnote explains that the man was Arthur Coga, said to have been a bachelor of divinity. Dr. King, who performed the experiment on November 23, 1667, wrote to Robert Boyle that Coga was about thirty-two years of age, and that his brain was "a little too warm."

On November 30, Pepys was

pleased to see the person who had his blood taken out. He speaks well, and did this day give the Society a relation thereof in Latin, saying that he finds himself much better since, and as a new man, but he is cracked a little in his head, though he speaks very reasonably, and very well. He had but 20*s*. for his suffering it, and is to have the same again tried upon him: the first sound man that ever had it tried on him in England, and but one that we hear of in France, which was a porter hired by the virtuosos.

Today a man would certainly have to be cracked a little in his head to permit transfusion with the blood of an animal in return for twenty shillings, or any other sum. The results were not only not encouraging, but in some cases actually disastrous, and the procedure was finally abandoned, not to be resumed until the necessity for matching the blood of the donor with that of the recipient had been realized.

Lower eventually settled in London, where he became one of the foremost practitioners of medicine. In 1675 he was appointed Court Physician, and no one was held in higher regard at the mad, merry Court of Charles II than Dr. Richard Lower. But as he was a Protestant he was deprived of his position upon the accession of that ardent convert to Catholicism, James II. The doctor died at his home in King Street on January 17, 1690, in consequence of a chill suffered while he was helping to extinguish a chimney fire that had broken out there.

The fourth member of that brilliant group of Oxford physiologists was John Mayow (1643–79), London-born and a lawyer until he became interested in experimental medicine. He was shy and sensitive, personal slights affected him deeply, and it has been suggested that his untimely death at the age of thirty-six may have been caused in part by the failure of his contemporaries to appreciate the significance of his work. Though a dissenting voice has been raised here and there, it is the consensus that he accomplished wonders in his short life. He gave a remarkably accurate description of the manner in which the intercostal muscles expand the chest by raising the ribs, and showed that expiration is but a passive result of their relaxation. Furthermore, he realized that the whole air is not essential to life, for when a small animal or a lighted candle was sealed in a closed vessel the animal died, or the flame went out, though most of the air still remained. Hence, he concluded, only a part of it is essential to life, or to combustion—two processes that appeared to be identical.

The substance that was attracting most attention from the chemists of his day was nitre—sodium or potassium nitrate, or saltpeter, as it is popularly called: a constituent of gunpowder that is not of itself inflammable but burns fiercely when mixed with sulphur. Nitre, said Mayow, had made as much noise in philosophy as it had in war. In the experiments described just above the animal or the candle represented to him sulphur, the combustible material, nitre being supplied by the air in the form of "igneo-aerial particles," or "nitro-aerial spirit." In fact Mayow had discovered oxygen, though that name was not acquired until more than a hundred years had gone by.

For Mayow the air was not a single substance, but a mixture in which the nitro-aerial spirit was present in limited proportion and gave the power of supporting life, or a flame; and it was this constituent that blood took from the air in coursing through the lungs. But in conformity with Descartes' hypothesis of vital spirits, widely accepted at the time, both Mayow and Lower thought that the nitro-aerial spirit is carried to the brain and thence to the muscles, for whose contraction it was believed re-

sponsible. An animal breathing in a closed vessel, or a candle burning under the same conditions, were known to cause a diminution in the volume of air contained, ascribed by earlier investigators to its "spring," and Mayow seems to have been the first to measure the extent of this decrease.

He had grasped the first principle of respiration: that a portion of the atmosphere is extracted by the blood as it makes its way through the lungs. But his work, like that of Lower, was neglected; partly because new ideas are generally unwelcome, but partly, too, because of the errors in a garbled English abstract of his Latin text that some literary hack had made for the Royal Society. As Sir Michael Foster wrote in his *Lectures on the History of Physiology*, the world had to wait more than a hundred years before Mayow's idea arose once more from the grave, as it were, in new dress and with a new name. That which flashed out in the middle of the seventeenth century as igneo-aerial particles and then died away again reappeared as oxygen more than a century later.[3, 4, 5, 16]

Further progress had been delayed in the meantime by the phlogiston theory. Developed by Georg Ernst Stahl, physician, chemist, and professor of medicine at Halle in his *Fundamenta chymiae* (1723), this taught that nothing is added during combustion and respiration; on the contrary, something called phlogiston escapes. Does not a burning candle grow shorter, and cannot expired air be seen on a cold day? Every combustible substance must contain phlogiston, and lose it during combustion, though in some cases the process was held to be reversible.

The error, caused by a failure to weigh and to measure, was exposed by Joseph Black, also a physician and chemist but of Scottish birth. During the course of some accurate quantitative experiments he rediscovered in 1754 a gas first isolated about 1640 by the Belgian chemist J. B. van Helmont, who had coined the word *gas* for this aeriform substance, calling it *gas sylvestre* because he had produced it by burning wood.

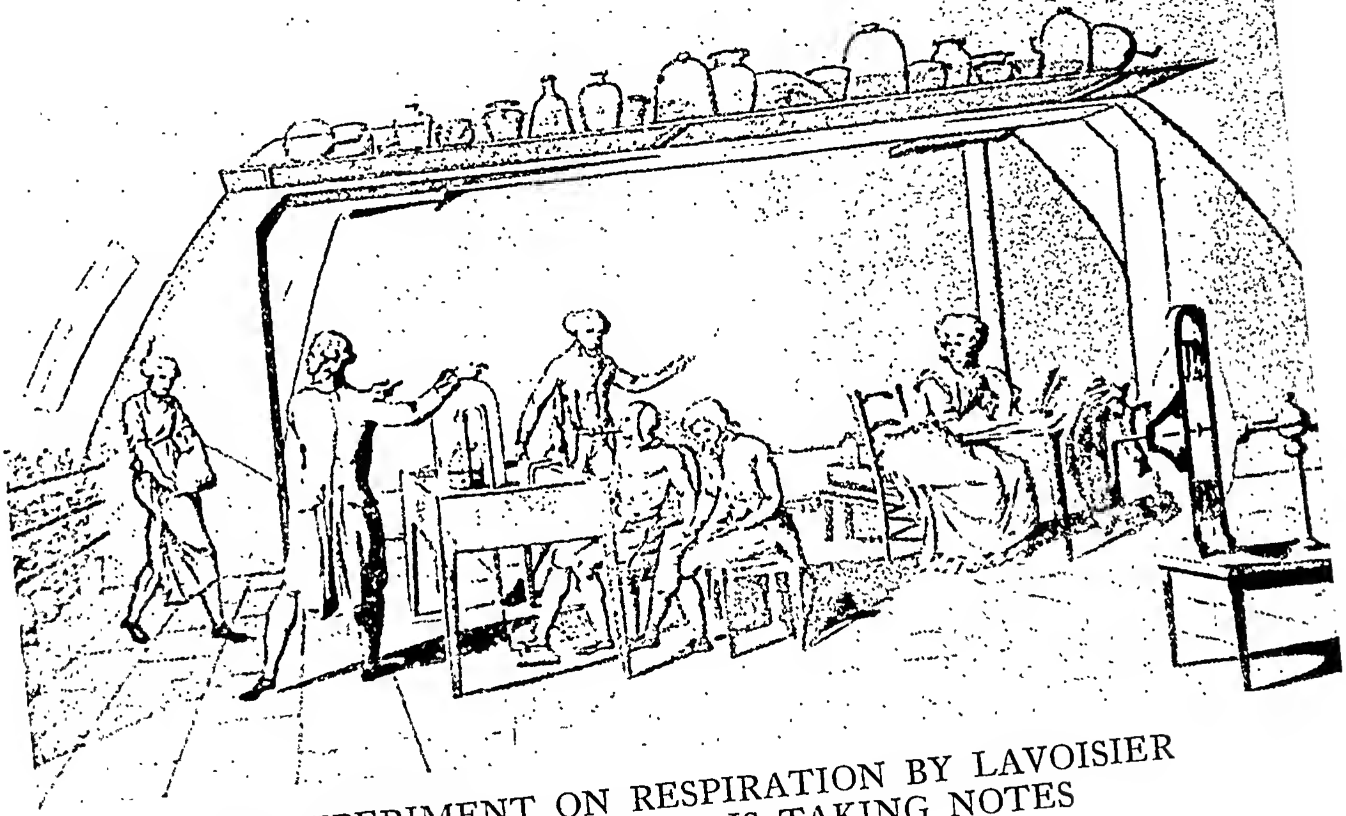
Black observed its formation when marble or chalk was heated, and named it fixed air from the fact that it is contained in these

solid materials. He noted also that it is a product of both combustion and fermentation, and present in expired air. It proved deadly to all animals exposed to it, and he convinced himself that the change produced in fresh air when it is breathed is a conversion of part of it into fixed air, or carbon dioxide as this gas is now called.[5, 14, 16]

The next step was taken by Joseph Priestley, an English clergyman who at one time made his home near a brewery—but only because its fermenting vessels were an unfailing source of the carbon dioxide with which he was then working. Born near Leeds in 1733, he was accused in later years of sympathy with the French Revolutionists and had to flee to America, where he died in 1804.

It is well known, he wrote, that a flame cannot subsist long without change of air, and that the quantity required to sustain it is enormous. He went on to ask what change is made in the constitution of air by the presence of a flame, and what provision there is in nature for "remedying the injury" that the atmosphere receives by this means. Since air is necessary for both plant and animal life he thought at first that the effect of deprivation would be the same for each, but was surprised to find that a sprig of mint confined in a glass jar that was inverted in a vessel of water to prevent the access of fresh air continued to grow for months. Furthermore, the imprisoned air would not extinguish a candle, and was not "inconvenient" to a mouse. Finally, air in which the flame of a wax candle had gone out would support combustion again after a sprig of mint had been growing in it for ten days. From all this he drew the conclusion that at least one of the agents capable of restoring "spoilt" air is vegetation.

Priestley actually prepared oxygen in 1774 by heating mercuric oxide and discovered many of its properties, including the power to support vigorous combustion and maintain animal life. Under the influence of the phlogiston theory, however, he named the new product "dephlogisticated air," failing to realize the enormous significance of his discovery. This great amateur chemist had found something that is used up in both respiration and ordinary combustion and given off by green plants, but it was



AN EXPERIMENT ON RESPIRATION BY LAVOISIER
MADAME LAVOISIER IS TAKING NOTES

left for Lavoisier to recognize the real nature of the newly isolated gas.[5, 16]

The death blow to the phlogiston theory was delivered by Antoine Laurent Lavoisier. The founder of modern chemistry was born in Paris on August 26, 1743, and in his youth, like Servetus, Mayow, and Lewis Carroll's Father William, he took to the law. Earlier still he had had an excellent training in science, and eventually deserted the legal world to return to the study of natural phenomena. But just as he seemed about ready to launch himself on a wholly scientific career he took the surprising step of accepting a responsible administrative post in the *Ferme Générale*, a wealthy company to which the government entrusted the collection of its revenue. Here he proved to be a capable man of business, and here he remained for twenty-three years, rising steadily to the position of *fermier générale*. Each day he put in enough time to get through his administrative work, which often involved much traveling, yet was able to give six hours to his scientific pursuits in addition.

In 1771 Lavoisier married Marie Anne Pierrette Paulze, a girl of fourteen, and though at the time he was just twice her age the marriage was a congenial one, for the young wife developed into a brilliant woman who was completely devoted to her husband and his work. An artist of no mean ability and a pupil of Jacques Louis David, renowned for his classical style, she illustrated Lavoisier's articles and shared otherwise in his scientific pursuits.

His wide interests including politics, he was appointed in 1775 an inspector of gunpowder for the government. But as if all this were not already enough he gave considerable time to education and prison reform, and maintained an experimental farm on his estate at Fréchine; for he was descended from peasant stock and never lost his interest in agriculture.

Toward the end of August, 1774, the month in which Priestley discovered oxygen without realizing that he had done so, the Englishman visited Lavoisier at his home and described the properties of the newly isolated gas, which he thought might

be that now called nitrous oxide. But the other amateur saw immediately that this was the clue he had been seeking to explain the results of his experiments on combustion. Lavoisier had found that when sulphur and phosphorus were burned they increased in weight because they absorbed "air," whereas the metallic lead produced from litharge, a form of lead monoxide, weighed less than the original litharge because it had lost "air." Knowing that in combustion only part of a given volume of air is used up, he realized at once that it was Priestley's new gas that was absorbed by phosphorus and other substances when they were burned. Eventually Lavoisier gave it the name oxygen, or acid producer, on the mistaken assumption that it took part in the formation of all acids. Combustion he referred correctly not to the liberation of the hypothetical phlogiston but to the combination of a burning substance with oxygen.

This active constituent of the atmosphere, "vital air," as he first called it, Lavoisier assumed to be involved in the lungs in a chemical reaction during which heat was set free, and he gave conviction to the hitherto unproved hypothesis that respiration is analogous to slow combustion. During respiration, he wrote, some vital air is taken into the blood and some is expired as carbon dioxide.

The similarity between respiration and combustion was shown in 1780 by Lavoisier and his collaborator, Pierre Simon Laplace, the famous mathematician and astronomer, by a comparison of the amount of heat generated when charcoal was burned to carbon dioxide and the amount lost by a guinea pig in producing the same quantity of this gas.

Applying what he had learned about respiration, Lavoisier insisted on the need for adequate air space where one or more persons were present, and pointed out the necessity of abolishing those dark subterranean chambers in which prisoners were confined. But this is not the only hygienic advance accredited to him. Though not a physician, he was the first to advise thorough bathing and the boiling of clothes as a protection against the transmission of infectious diseases by those suspected of harboring them. He inaugurated schemes for street-lighting, too; introduced im-

provements in agriculture; assayed the nutritional worth of different kinds of food; and, with Benjamin Franklin and other illustrious scientists of his time, investigated the value of mesmerism.

But the Ferme was anathema to the nation in its new revolutionary mood and in March, 1791, it was suppressed by decree of the National Assembly. Unjust accusations were hurled against its former members, who were arrested and imprisoned on November 14, 1793. Long delays followed, with attempts to obtain their release, and not until May 2, 1794, were they brought before the Revolutionary Tribunal for trial—that trial at which the prosecution declared: "The Republic has no need of savants. Justice must take its course." But it was gross injustice that took its course instead, for six days later Lavoisier and twenty-seven of his companions met death under the guillotine in the Place de la Révolution. "It took only a moment to cut off that head," said Joseph Louis Lagrange, famous astronomer and mathematician, "but it may be a hundred years before we see such another."[6, 17]

All these discoveries in respect to the chemistry of respiration raised two main questions. What is it that is oxidized, and where does the reaction take place? The first was easily answered: it is the food.[6] The second was not so simple, however, and doubt ruled for many years. Lavoisier had proved that oxygen combines with carbon in the living body to produce carbon dioxide, just as it does during combustion, and that the reaction is the source of animal heat. But, like his predecessors, he made the mistake of assuming that this combination occurs in the lungs. The error was corrected in 1791 by Lagrange, who maintained through his pupil Hassenfratz that not the lungs but the other tissues are the site of the change.[4] Almost fifty years passed, however, before technical advances in chemistry made it possible to prove that oxidation—which may be simply defined here as an increase in the proportion of oxygen by addition of this element or the removal of hydrogen—does not take place in the lungs. The truth appeared with the discovery that the blood leaving

them carries less carbon dioxide and more oxygen than that arriving there, whereas the reverse would be true if carbon dioxide were produced in the lungs.[18] Nor does the union of carbon and oxygen take place in the blood, for in its passage from the lungs to and through the heart it was shown to lose none of its oxygen and to acquire no carbon dioxide. It is in the systemic capillaries, all those of the body with the exception of the lungs, that the change is now known to take place. During its short stay of about one second in these vessels the blood parts with some of its oxygen and takes up an equal volume of carbon dioxide from the cells of muscles, glands, and so on. The crimson stream is not a consumer but only a carrier of oxygen, which is not simply in solution there but held in loose chemical combination by the pigment that gives its red cells their color: hemoglobin.

When it was realized that the cells of the various organs and tissues are the true seat of oxidation, chemists began to speak of internal respiration and to compare it with external respiration, or the mere act of breathing.

Though the former is often likened to combustion, there is at least this important difference.[18] In a furnace under forced draft more oxygen is provided, more heat liberated, and more work done by the engine in consequence, provided all the other conditions remain equal. But the amount of oxygen supplied to the body does not determine the work done by its various members. On the contrary, their activities dictate the amount of oxygen to be consumed. As this enters the cells and combines with the food that they have assimilated, setting free their waste products at the same time, the miracle that is life goes on. For the organism is more knowing than any chemist. It is able to complete all these difficult reactions at a temperature of only 98.6° F., whereas compounds like sugar, starch, and fat must be heated to several hundred degrees if they are to be oxidized outside the body. The transformation is made possible in living cells by their enzymes, complex agents of a nature still only partly determined that accelerate the reactions almost as if by magic.

External respiration proceeds under ordinary circumstances without conscious effort. Why? In 1811 César Legallois found

that when he destroyed a certain part of the medulla oblongata, the posterior region of the brain where it tapers off into the spinal cord, the animal stopped breathing and death ensued.[6] The action of this group of nerve cells, now known as the respiratory center, is partly automatic but partly, too, under voluntary control, as is shown by the fact that breathing can be made faster or slower at will, or even suspended entirely for forty seconds or more. During this period, however, carbon dioxide is accumulating, and when the alkalinity of the blood has fallen to a definite point the respiratory center is stimulated by the change in reaction and a deep, involuntary inspiration follows. The automatic alarm has been sounded.

IV

THE FOXGLOVE

READERS of George Eliot may perhaps recall that Silas Marner had inherited from his mother some acquaintance with medicinal plants; a little store of wisdom imparted to him as a solemn bequest, and that in consequence he delighted to roam the fields in search of foxglove and other healing herbs. One day, taking a pair of shoes to be mended, he saw the cobbler's wife seated by the fire and suffering from the dread symptoms of heart disease and dropsy that had preceded his mother's death. Mindful of the relief that she had experienced from a simple preparation of foxglove, he promised Sally Oates to bring something that would ease her distress, since the ministrations of the local practitioner had been of no avail.

For some years before the novel opens, at the beginning of the nineteenth century, country folk in the heart of England—in Shropshire, in Warwickshire, and in the western part of Yorkshire—had known that dropsical complaints can be relieved with foxglove tea, but how this first came to light, or who made the discovery, will remain forever an impenetrable mystery.

The plant had been in use for centuries as an expectorant, and in earlier days was confidently relied upon to "scoure and clense the brest" by cutting and consuming "the thicke toughness of grosse and slimie flegme, and naughtie humours." [11] By the end of the sixteenth century many additional virtues had been ascribed to it and it was administered for everything from abscesses to epilepsy.

What more probable than that some of those who sought relief from naughtie humours or other distressing conditions should have been afflicted with dropsy, which in appropriate cases was relieved by foxglove? Such a striking event could not possibly have escaped notice, or failed to excite wonder through-

out the countryside, until at last foxglove came to be the mainstay of domestic medicine in the treatment of dropsical accumulations.

The fact that it sometimes failed, later in the hands even of the physician himself, was wrongly attributed by Erasmus Darwin, grandfather of the great naturalist and one of the foremost medical men of his day, to the unusually serious nature or advanced stage of the disease. "When Alcibiades walked over the temple of Neptune, and was shewn, by the priest, the numerous tablets suspended on the wall, by those who were saved from shipwrecks, he asked, scoffingly, 'where are the pictures of those who were drowned?' and was answered, 'the storms were so great, and so frequent, that it was not in the power of his deity to save them all.' "[2]

The fact is that dropsy, believed in Erasmus Darwin's time to be an independent disease, is only a sign after all, the serous fluid collecting in the various tissues or cavities of the body because there is grave trouble elsewhere. In the tissues beneath the skin, where the accumulation is called edema if localized or anasarca if widespread, it may point to a disorder of the heart or the kidneys; in the peritoneal cavity, where it is known as ascites, it may be associated with either of these two causes or with cirrhosis of the liver; in the lungs or the pleural cavities it may be an indication of heart disease or some other serious illness; "water on the brain," or hydrocephalus, is an outcome of inflammation or malformation of its membranes; and so on. But before all this was realized foxglove was prescribed for conditions that it could not by any possibility relieve, much less cure: to disperse the fluid of an ovarian cyst, for example.

It would have been curious indeed had foxglove not been tried in folk medicine, for it thrives like a weed throughout many parts of Europe and, as Kipling wrote:

> Anything green that grew out of the mould
> Was an excellent herb to our fathers of old.

It is common in dry, hilly pastures, in rocky places, and along roadsides and John Burroughs, the great American naturalist,

thought it the most beautiful and conspicuous of all the wild flowers that he had seen in England; his own country, he said, had nothing to compare with it.[8]

But it has been naturalized here, as anyone with a garden knows. One of the first to cultivate it must have been Dr. Hall Jackson, a physician of Portsmouth, New Hampshire, who wrote on April 30, 1787, to Ezra Stiles, President of Yale College:[10]

. . . In the last Ship from London, and the last Post from Boston, I was honoured with a very polite, obliging, and interesting Letter from Doctor Withering; and favoured, also: with a quantity of Seeds of the Foxglove by him. He writes, "*I send more than you may have occasion for, in the hope that you will distribute them into the other Provinces.*" It is with much pleasure I comply with the Doctors humane wish, in inclosing you a small quantity of them, being fully perswaded you will find equal satisfaction in the cultivation of so useful and ornamental a vegetable, it bears a beautiful purple Bell-Flower, worthy a place in any garden. . . .

I would just mention that it is a biennial plant, and I conclude it will take some little care to preserve the Roots from the severity of the frost in this cold climate, tho' it flourishes spontaneous in the fields of England.

My good intentions must be my apology, in the liberty I have taken in troubling a Gentleman of your character, with so lengthy a Letter, altogether professional, I wish to promulgate a valuable acquisition in Medicine, and am so unfortunate as not to be acquainted with any Gentlemen of the Faculty in your State.

My most respectful compliments waits on your Family.

I am Sir, with the utmost veneration and
respect! your most humb! Serv!
Hall Jackson

Dr. Stiles

[Endorsed]
Rec^d May 28 1787
Ans^d July 14 1787
Sowed the seed about June 6 1787. in my Garden

It is not without interest to note in passing that the good doctor's letter took nearly a month to cover the distance between Portsmouth and New Haven.

The blossoms of the foxglove have suggested many of its popular names throughout Europe. In Great Britain and Ireland it is called folk's-glove (i.e., fairies' glove), bloody fingers, ladies' thimbles, fairy thimbles; in France, gloves of Our Lady, fingers of the Virgin; in Germany, *Fingerhut* (thimble); and in 1542, because of this resemblance, Leonhard Fuchs, German physician and botanist, gave to this stately plant its scientific name: Digitalis.

Chance, said Pasteur, favors only the prepared mind, and to the everlasting benefit of the human race a prepared mind was there, ready to grasp the significance of the discovery made by the simple country folk.

William Withering was born at Wellington, Shropshire, in 1741, into a medical family. His father, Edmund, was a physician, and two brothers and a cousin of his mother, nee Sarah Hector, followed the same profession, as did George Hector, her father. Of him Samuel Johnson wrote: "My mother had a very difficult and dangerous labour, and was assisted by George Hector, a man-midwife of great reputation. I was born almost dead, and could not cry for some time. When he had me in his arms he said: 'Here is a brave boy.' "[13]

Edmund Withering, a man of prepossessing exterior, agreeable manners, and wide professional repute, fell victim to his humane exertions in November, 1769, during an epidemic the nature of which is not specified by William Withering's son and biographer. The widow survived him by nearly twenty years, dying July third, 1789, at the age of eighty-one.

William received his early education from his parents and from the Rev. Henry Wood, a neighboring clergyman, and as no anecdotes have come down from his boyhood days it may be inferred that, like so many other great men, he was not remarkable for precocity.

In the autumn of 1762 he matriculated at Edinburgh University, where he proved an industrious student of lively and vigorous intellect, who often consumed far more than his share of the midnight oil and participated actively in the meetings of the undergraduate medical society. Nor were the social graces

neglected; he joined a Masonic lodge, enjoyed golf and archery, performed skillfully on the flute and the harpsichord, and even learned to play the bagpipe—an unusual accomplishment, surely, for an Englishman.

Midway in the course he wrote to his parents: "The Botanical Professor gives annually a gold medal to such of his pupils as are most industrious in that branch of science. An incitement of this kind is often productive of the greatest emulation in young minds, though, I confess, it will hardly have charm enough to banish the disagreeable ideas I have formed of the study of botany." [12]

It seems remarkable that such a statement should have been made by a youth who was destined to become one of the greatest of botanists, and author of a textbook that enjoyed wide popularity all through the first half of the nineteenth century, but so it was.

The Shropshire lad passed his final examinations with credit, was admitted to the degree of Doctor in Physic on July 31, 1766, and, returning from a trip to the Continent in time to participate in the Christmas festivities at home, settled down to practice immediately afterward in the little town of Stafford. "Being neither deficient in perseverance or activity," as he himself remarked, he "would not willingly spend his life in preparing to begin to live. . . ." [12] Here his musical talents contributed to the amateur concerts that occasionally followed the pleasures of the bowling green at Wolseley Bridge, and he joined an amateur dramatic society, for a love of the theater had been born in him when, during his student days, he spent some months in London.

The suggestion has been made that Withering's early indifference to botany may have been overcome partly through his friendship with Richard Pulteney, a friend of his university years and later a Fellow of the Royal Society and author of *Historical and Biographical Sketches of the Progress of Botany in England*. But who will not prefer the alternative explanation, that it was through his desire to secure specimens for Miss Helena Cookes to draw and that the great transformation was wrought by her bright eyes?

She was one of his first patients and, having re-established her health and been admitted to habits of intimacy with her family, he says, he was permitted in some degree to direct the completion of her education. "The harpsichord, the voice, the pencil, and every exterior accomplishment were already at her command"; his duty was to extend her taste for literature.[12] This he may well have been able to do for he was a lover of poetry, especially that concerned with scenery, and in fact had published anonymously some efforts of his own, though in the eyes even of his son these were of no great merit and displayed more the art of the scholar than the fire of the born poet.

The following example, quoted by Capt. L. H. Roddis in his biographical sketch,[8] shows Withering to have been far greater as a physician than as a versifier.

> The foxglove's leaves, with caution given,
> Another proof of favouring Heav'n
>   Will happily display;
> The rapid pulse it can abate;
> The hectic flush can moderate
> And, blest by Him whose will is fate,
>   May give a lengthened day.

The young physician and his former patient were married on September 12, 1772, and as a consequence he began to look about him to find a means of widening his practice, for at the end of five years he was earning scarcely £100 annually. Three years passed by, however, before a suitable opportunity presented itself; then, in May, 1775, he settled in Birmingham though he continued to serve the Stafford Infirmary, which he had been largely instrumental in establishing, by making a weekly journey of almost sixty miles until a successor could be chosen. Toward the close of the year the loss of a first-born infant was compensated by the birth of his son, William; the only other child was a daughter, Charlotte.[12]

Even then Birmingham was a busy manufacturing center, and within a year his income had more than doubled and soon amounted to £1,000, or more than he had made during his whole

eight years in Stafford. By 1778 he was said to have the largest practice outside London, and before long was being sought as a consultant throughout a large part of western England and Wales.

But his increased exertions were not made without sacrifice of his own health. As early as 1776 he was suffering from an indisposition that, in his own words, prevented his "doing anything or thinking of anything which could be avoided: an irregular sort of fever . . ." that lasted for three weeks. It was the prelude to many more serious attacks and, indeed, the severity of winter always deprived him in some degree of his accustomed energy. Nevertheless, he continued to work on his great textbook: *A Botanical Arrangement of All the Vegetables Growing in Great Britain, According to the System of the Celebrated Linnæus; with an Easy Introduction to the Study of Botany*, which issued from the press in the summer of 1776.

No sooner was it finished than he began to engage in other scientific pursuits. He had already devised an instrument for the accurate drawing of perspective, and a microscope, more portable and convenient than any previously constructed, for examining minerals and the minuter portions of plants, and now he translated Bergman's *De Analysi Aquarum*, illustrating it with many additional remarks. As an exercise in the art of analyzing water he tested several mineral springs, and compounded in exact imitation the waters of several others. He managed to find time, also, for music and mineralogy, for antiquarian matters and the keeping of meteorological records, for geology and the improvement of electrical apparatus, and for studies on the nature and properties of air. Naturally enough his activities varied with the seasons, and on one occasion he wrote, before the setting in of winter: "Botany now no longer presides at my board,—her season is past,—and chymistry overspreads the table . . ."

At Birmingham he found a congenial circle in the Lunar Society, whose harmony and diligence, says his son, nothing could exceed until, in an unhappy crisis, political discussions were allowed to invade the fairer province of science. Here Withering met such distinguished men as Matthew Boulton, the great

manufacturer; Joseph Priestley; James Watt; Erasmus Darwin; Samuel Galton; and Josiah Wedgewood. The members, interested in all branches of science, gathered every month in each others' homes and always at the full of the moon, whose kindly light was depended upon to lead them in safety over treacherous roads to and from the meetings.

In his constant endeavor to promulgate knowledge and correct error Withering took considerable pains to ascertain how far the prevalent opinion that the moon's phases influence the weather was consistent with fact. He fully refuted this idea by a series of observations continued throughout the year 1780, proving that "of thirteen new moons only five were accompanied by any change of weather; and that of twelve full moons, only four, or at most five, were noted for any alteration." In a footnote his son says that this fallacy was exposed also by the Rev. William Gregor, of Cornwall, whose observations from January, 1765, to the end of 1782 led to a similar conclusion.

By 1782 Withering's attainments in science were so widely recognized, not only by his professional and scientific friends but by many laymen in the neighborhood, that any sort of natural object thought to be of unusual interest was brought to him for examination. His biography contains an amusing story of a country laborer who showed him a stone closely resembling the human heart in both size and shape, which the good man, in a literal interpretation of Holy Writ, believed was the heart of a Pharaoh, hardened by the Lord, as related in the book of Exodus.

But Withering's talents received more formal recognition in 1784, when he was elected a Fellow of the Royal Society.

During the winter of 1783 his researches were interrupted by a severe pulmonary complaint, yet he continued to labor on at his profession from November until March, when the threat to his health was no longer to be neglected and to save his own life he had to forego for a time the care of others. Slowly his condition improved and he was left with only a slight cough, which he expected the approaching summer would remove. In the following year he retired to the country for several months in order that he might avoid the smoke of Birmingham; feeling

better toward fall he resumed his practice, and the end of that year found him hard at work on a new edition of his botany.

The revision was interrupted in 1785 by requests from his friends that he publish his observations on foxglove, which was being so unskillfully used that it was regarded in certain quarters as a virulent poison; furthermore his friends feared that some of those to whom he had taught its proper use might claim the credit for their own. The modesty and transparent honesty of the man come to light in the first few paragraphs of his Preface to the little volume that resulted: *An Account of the Foxglove and Some of Its Medical Uses: with Practical Remarks on Dropsy and Other Diseases.* One of the greatest of medical classics, it contains his observations on 163 of his own patients, to which are added a number of case reports from other physicians.

After having been frequently urged to write upon this subject, and as often declined to do so, from apprehension of my own inability, I am at length compelled to take up the pen, however unqualified I may still feel myself for the task.

The use of the Foxglove is getting abroad, and it is better the world should derive some instruction, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable.

It is now about ten years since I first began to use this medicine. Experience and cautious attention gradually taught me how to use it. For the last two years I have not had occasion to alter the modes of management: but I am still far from thinking them perfect.

It would have been an easy task to have given select cases, whose successful treatment would have spoken strongly in favour of the medicine, and perhaps been flattering to my own reputation. But Truth and Science would condemn the procedure. I have, therefore, mentioned every case in which I have prescribed the Foxglove, proper or improper, successful or otherwise. . . .

. . . the instances I am going to adduce, may truly be considered as cases lost to the common run of practice, and only snatched from destruction, by the efficacy of the Digitalis; and this in so remarkable a manner, that, if the properties of that plant had not been discovered, by far the greatest part of these patients must have died.

The virtues of animal and vegetable substances, he continues, must be learned

> either from observing their effects upon insects and quadrupeds; from analogy . . . or from the empirical usages and experience of the populace.
>
> The first method has not yet been much attended to . . . the last, as far as it extends, lies within the reach of everyone who is open to information, regardless of the source from which it springs.
>
> It was a circumstance of this kind which first fixed my attention upon the Foxglove.
>
> In the year 1775, my opinion was asked concerning a family receipt for the cure of the dropsy. I was told that it had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed. I was informed also, that the effects produced were violent vomiting and purging; for the diuretic effects seemed to have been overlooked. This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant in these subjects, to perceive, that the active herb could be no other than the Foxglove.

Withering first used a decoction of the leaves; then, for fear that boiling might destroy their activity, an infusion. In the summer of 1776 he began to employ the dried leaves, "and as it then became possible to ascertain the doses" these were gradually adopted by the physicians of his immediate acquaintance. ". . . but I wish it not to be tried in the ascites of female patients, believing that many of these cases are dropsies of the ovaria; and no sensible man will ever expect to see these encysted fluids removed by any medicine."

At length, in the year 1783, foxglove appeared in the new edition of the Edinburgh Pharmacopoeia, "from which, I am satisfied, it will be . . . very soon rejected, if it should continue to be exhibited in the unrestrained manner in which it has heretofore been used at Edinburgh, and in the enormous doses . . . now directed in London."

The author clearly describes the indications for its employment, and heartily condemns the large doses prescribed by those who were unfamiliar with its dangers. Thus Dr. Cawley, of

Brasenose College, Oxford, was given twelve times the amount that a strong man ought to have taken, and "if he had not had a constitution very retentive of life . . . must have died from the enormous doses he took." "Shall we wonder then that patients *refuse to repeat* such a *medicine*, and that practitioners tremble to prescribe it? Were any of the active and powerful medicines in daily use to be given in doses *twelve* times greater than they are, and these doses to be repeated without attention to the effects, would not the patients die, and the medicines be condemned as dangerous and deleterious?—Yet such has been the fate of Foxglove!"

Naturally enough the country folk were using it even more unskillfully. ". . . I recollect," wrote Withering, "about two years ago being desired to visit a travelling Yorkshire tradesman. I found him incessantly vomiting, his vision indistinct, his pulse 40 in a minute. On enquiry it came out that his wife had stewed a large handful of green Foxglove leaves in half a pint of water and given him the liquor which he drank at a draught, in order to cure him of an asthmatic affection. This good woman knew the medicine of her country, but not the dose of it, for her husband narrowly escaped with his life."

Withering's book was not the first printed account of the use of foxglove.[4] Erasmus Darwin's eldest son, Charles, who died before reaching the age of twenty from septicemia in consequence of having cut his hand while performing an autopsy, was credited with having described its therapeutic effects five years before Withering. Dr. John F. Fulton believes that this report was added to the manuscript by his father, who no doubt had learned of foxglove from Withering; and that whereas mere priority of publication should therefore go to Erasmus Darwin, who supplied the note in his son's manuscript, it was Withering who actually inaugurated the systematic use of the drug and convinced his medical contemporaries of its value.

Withering could not differentiate the dropsy of heart disease from that associated with disorders of the kidney, nor could any other physician of his day; more than forty years were to pass before Richard Bright made this distinction. Hence the standard

treatment for any dropsy was the administration of diuretics to increase the flow of urine, in the hope that the excess fluid would thus be carried off. Withering repeatedly emphasized the diuretic effect of foxglove, attributing its beneficent action chiefly to this; he did not understand that its results are accomplished by its effect on the heart and the blood vessels, especially those of the kidney, though he did notice that it had a favorable action on the heart such as was exerted by no other medicine. But the specific effect of digitalis on the cardiac muscle was not revealed until the middle of the following century.[5]

Withering was far ahead of his time in more ways than the one we have been discussing until now. He insisted that pulmonary tuberculosis can be passed from one person to another, and that the strict laws then operating in Italy to prevent consumptive patients from infecting others had not been enacted without sufficient cause.[11] Furthermore, he strongly recommended that, in order to prevent rabies, dog bites be thoroughly washed out and then treated with a caustic, a procedure that is still an important part of their treatment today.[9]

By the time his book on the foxglove had appeared Withering's incessant exertions of mind and body had begun to impair his natural vigor. He had long been convinced that he had "embraced an anxious and a slavish profession; in which the most successful are better rewarded by the consciousness of doing good than by its most ample emoluments." [12]

In this year, 1785, he traveled 6,353 miles on his rounds, over the miserable roads of the day, but the long hours were not unprofitably spent for he read and wrote much, aided in the dreary nights of winter by a light that he had installed in his carriage. On one occasion, a few years previously, when his horses had become unmanageable, he had imprudently leaped from the vehicle, and the consequent fracture of a collarbone and concussion of the brain had disabled him for several weeks.

In order to escape the smoke of Birmingham Withering moved, in 1786, to Edgbaston Hall, a spacious suburban mansion surrounded by a park that afforded an interesting combination of woods, water, and undulating lawns. The approach of summer

banished in great degree the complaints that had been aggravated by the preceding long winter, but his exertions had so weakened him that he seldom passed many months without experiencing more or less trouble with his lungs.

His reputation as a physician, a scientist, and a man was now at its height. Already complimented in Germany by having a mineral named witherite in his honor, he received still further recognition when the distinguished French botanist, l'Héritier de Brutelle, opened the first fasciculus of his *Sertum Anglicum* by naming a genus of plants *Witheringia solanacea.* From Russia and from Holland the meed of praise flowed in the most gratifying way, while from America he received assurance through the pen of Dr. Hall Jackson that "thousands were wishing to offer their tribute of gratitude" for his indefatigable endeavors in the interest of mankind. Many patients from London and other parts of Great Britain and Ireland regularly sought him out, and not a few invalids in Paris wrote for his advice, among them the venerable Benjamin Franklin, who addressed to him an inquiry concerning urinary calculi.

In the spring of 1790 Withering suffered severely from his pulmonary complaint, and the cold winds of March and April retarded his convalescence. In the following year, said his son, the same "trying season" brought renewed suffering. The English spring must have changed its character by the time Browning wrote:

> Oh, to be in England,
> Now that April's there!

On May 16 he had a severe seizure, and from that time on his existence was but a struggle against the unrelenting inroads of disease, though his mind continued energetic and he resolutely persevered in his active duties.

A misfortune incurred at this time caused further deterioration in his health. Under the teachings of Edmund Burke impatience against the excesses of the French Revolution had been growing in England, and a dinner given in Birmingham on July 14, 1791, to celebrate the fall of the Bastille was the occasion of grave rioting. Neither Priestley nor Withering attended; never-

theless a mob, inspired by the rising hatred against all radicals, domestic or foreign, sacked the house of the former because of his well-known sympathy with the revolutionists. Withering, who had mildly favored their cause for a time, was informed that his home, also, would be destroyed. His neighbors rallied about him and several risked their lives in an attempt to repel the incendiaries, but no sooner had one party been beaten off than another came forward and the damage was limited only by the timely arrival of a military force. In his critical state of health Withering was forced to flee and by this sudden removal his books and collections, covered with straw in wagons that were driven through the roughest and least frequented lanes, sustained material damage. One hundred and fifty pounds might have repaired the injury to his house, but nothing could compensate for the mischief done to his library, to his herbarium, and above all to his health, which by now was seriously threatened. Toward the end of the year he began to consider retirement to a warmer climate.

But Lisbon, where he spent the two following winters brought him so little relief that he resolved to risk the ensuing winter in England. His symptoms closely resembled those of pulmonary tuberculosis, and it was taken for granted by Withering himself and by the colleagues who attended him that he was afflicted with this disease. Modern clinicians, however, believe that his trouble was not tuberculosis but bronchiectasis,[6, 7] a condition in which the secretions accumulate in dilated bronchial tubes and ultimately become infected by bacteria inhaled with the air; if tuberculosis were present at all, it is said, this must have been a secondary infection. But the diagnosis of bronchiectasis could not have been made in Withering's day because the disorder remained unknown until some twenty-five years after his death.

His distress was greatly mitigated by the artificial climate that he maintained in his spacious library at Edgbaston Hall, which he furnished with double sashes, heated by flues, and kept at a constant temperature of 65° F. Avoiding all unnecessary effort, since activity caused his fever to rise, he spent his days of seclusion in rewriting his textbook.

Finally convinced that the exposed situation of Edgbaston Hall was injurious to him, he bought a home in a more sheltered location on the outskirts of Birmingham. The fatigue involved in superintending its repair and getting ready to move might in itself have been borne without too much danger, but at the same time he was undergoing the greatest anxiety by reason of an alarming illness in his wife, and removal to the new home on September 28, 1799, was made peculiarly sad by her inability to accompany him. She parted from him under the grievous impression that she should see him no more in this world.

On October 2, when his condition was serious, the venerable Lord T—— arrived, with an introduction that the doctor could not altogether neglect, though confined to that bed from which he was never to rise again. Physician to the last, Withering traced with extreme difficulty a few notes on a plan of treatment, and by this act closed his career as a practitioner of medicine.

Early on the morning of Sunday, October 6, 1799, his spirit (the words are Kipling's) received permission.

Withering was somewhat above the average height, and until bowed down by ill health might have been described as robust rather than otherwise. The best-known portrait, said by a lifelong friend to be a perfect likeness, shows that his features were exceptionally regular save for the nose, which was a trifle too long. His habitual neatness was reflected in his dress no less than in his handwriting, which was far above the illegible scrawl of so many physicians. He was affable, though with a slight touch of reserve; domestic in his tastes and deeply attached to his wife and children; modest; a man of the strictest integrity; and a devout member of the Church of England. Tender and sympathetic toward the poor, of whom he saw between two and three thousand annually, as he was to all who sought his care, he applied every means within his power to relieve their suffering. Botanist, mineralogist, chemist, antiquarian, he was first of all the beloved physician.[1]

As he lay dying a friend exclaimed: The flower of English medicine is Withering.

V

VACCINATION

That disease over which science has since achieved a succession of glorious and beneficent victories, was then the most terrible of all the ministers of death. The havoc of the plague had been far more rapid: but the plague had visited our shores only once or twice within living memory; and small pox was always present, filling the churchyards with corpses, tormenting with constant fears all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden objects of horror to the lover.

Thus did Macaulay write of this filthy disease in describing the death of the young and blooming Mary II, Queen of England and consort of William III.

During the next century sixty million Europeans succumbed to smallpox, so called originally to distinguish it from the great pox, or syphilis. Among them was Louis XV, of France, for palace and hovel suffered alike. No mother counted her children until they had passed through the smallpox; an early German writer facetiously remarked that few escaped smallpox and love; and young men sighed for a mistress whose face was not pockmarked.

This river that everyone had to cross, in the words of an eighteenth-century writer,[19] was present in Egypt and India in remote times, but because primitive transportation was slow it did not reach Europe until about the tenth century, and five hundred years went by before it was well distributed there. The first great London epidemic broke out in 1628.[12] Early in the sixteenth century the Spaniards introduced the disease into Mexico, where it destroyed three and a half million persons within a short time and whence it spread to the North American Indians, half of

whom perished. Not to be niggardly in the matter the Indians passed it on to the New England colonists, and six epidemics visited Boston; in that of 1721, for example, half the inhabitants were stricken.

All in all, more than 80 per cent of mankind were attacked, and one fourth of every nation disfigured, crippled, blinded, or killed.

If the constant vigilance of health officers were to be relaxed for a moment, or if those who do not "believe" in vaccination were to have their way, there is not the remotest doubt that these terrible scenes would be repeated. There are still many unvaccinated persons throughout the world, some of them in the most civilized countries thanks to a misguided tolerance, and vast reservoirs of the disease in other lands where it only waits its chance. Watches and waits.

Rolleston and McClean say that the two chief plague spots in Europe are, or were in 1939, Soviet Russia, in which smallpox is of the virulent type, and the Iberian peninsula, where it is usually mild in Spain, severe in Portugal. In North Africa the danger spot is Egypt, with between five and six thousand cases in 1933 and one thousand deaths. But the most important focus in the world is India and, indeed, the whole Orient reeks with smallpox. Lest it be thought that the situation may have improved since these figures were compiled, it may be said at once that in 1946–47 there was an epidemic in Rangoon with a death rate of 30 per cent, and another in Hong Kong at the same time in which 530 out of 820 patients died, a mortality of 65 per cent. According to the United States *Public Health Reports* there was smallpox in at least 89 countries during the period January–September of 1946, from one case in some up to 57,378 in India.

In North America the most dangerous center is Mexico, where the disease is of the virulent type. As for the United States and Canada, smallpox has been present for years but by good fortune it is usually mild, though the severe kind is by no means unknown. It appeared in New York City in the spring of 1947, having been brought in by a traveler from Mexico, and there were twelve cases with two deaths. There would have been many

more had it not been for an extraordinarily efficient Department of Health, and an enlightened populace who stood in line literally by the million to be vaccinated.

Macaulay's picture was not overdrawn. Sir Matthew Hale, a Lord Chief Justice of England in the seventeenth century, wrote that a person with smallpox was "in the very next degree to absolute rottenness, putrefaction, and death itself." It was more virulent in his day, yet even now the disfigurement caused in severe cases by the extensive eruption and edematous swelling of the face is unparalleled among the acute infectious diseases, and many appalling examples were seen by Rolleston and McClean among infants and young women in the London epidemic of 1901–2. As if this were not enough, the repulsive condition of these unfortunates is heightened by a disgusting odor.

The virus responsible for smallpox, or variola as it is called in medicine, is thought to be carried from person to person by droplet infection and to enter the body by way of the respiratory tract.[20] That is to say, minute particles of mucus and saliva projected into the air by the patient in talking, or much farther in coughing, are inhaled by those near by. Thus in general the area of danger is the immediate vicinity of the patient himself, though as the virus may remain infectious for long periods after drying, soiled clothing and dust must be taken into consideration.

From ten to seventeen days after exposure, but usually twelve or thirteen, one who has caught the disease suddenly begins to feel ill, with shivering, a rapid onset of fever, headache, vomiting, pain in the limbs, and a really severe backache that is highly suggestive of smallpox though not of invariable diagnostic value. A rash resembling that of measles, scarlet fever, or hives may break out, but it has no characteristic features and the typical eruption does not appear until the third day. When it does the patient feels much better and the temperature, called the primary fever, which may have been as high as 104°F., comes down.

The specific eruption takes the form of macules, or spots, about the face, head, and wrists and soon spreads to the rest of the body, though the parts exposed to light are always most deeply involved. Within a few hours these macules become raised from

swelling and proliferation of the infected cells at the site of each one, and so hard that they feel like shot under the skin; the eruption is now said to be papular. Three days more and the papules fill with a clear, watery fluid. When fully developed they are *characteristically multilocular* and *umbilicated* or, in other words, consist of several small cavities each and have a central depression. Finally the contents of these little blisters, or vesicles, turn to pus from death of their infected cells, and with this formation of pustules the temperature rises again, except in mild cases, to constitute the secondary fever. On the tenth day of the eruption or thereabouts the pustules either rupture or dry up, leaving scars, or pits, which are deep in proportion to its severity.

When the pocks are separated by areas of healthy skin the disease is called discrete smallpox, confluent when the lesions are so abundant as to run together. In the former, which is a mild type, complications are few and the death rate hardly exceeds 1 per cent, as in the 45,000 cases in North America in 1902, whereas in confluent variola it may rise to 60 per cent, as it did in the epidemic of 1918 at Rio de Janeiro. The most dreaded of all is hemorrhagic, or black, smallpox, with its bleeding into the skin *and from all the body orifices; this type is uniformly fatal.*

The mild disease, variola minor, or alastrim, is a variant of smallpox and not new, having been observed in the seventeenth century by Sydenham and in the eighteenth by Jenner. It does not give rise to the severe form and has a low degree of infectivity, for a single case may occur in a large household without infecting any of the other members, even though all be unvaccinated.

Variola minor is distinguished from varioloid, a modified and mild smallpox seen in those who have been vaccinated or have had smallpox, but in either case too long in the past to enjoy complete immunity.

Since the eruption of smallpox involves the mucous membranes and internal organs as well as the skin, though in modified form, there are many other accompaniments of the disease, such as sore mouth, sore throat, and laryngitis, for example. Sometimes the larynx is so swollen by edema as to cause death by suffo-

cation unless the patient be instantly relieved by opening the trachea. Indeed, the complications of smallpox are worse than the disease itself. Commonest of all is bronchitis, which is often followed by bronchopneumonia that may prove fatal. Areas of bone marrow may die and the growth of a bone be checked in consequence, with shortening of the limb as a final outcome; or essential organs like the liver, kidneys, and heart may be seriously damaged. Then, too, there is an intimate association between variola and the pus-forming organisms, so that suppurative inflammations of the middle ear, boils, abscesses in the skin and underlying tissues, or septicemia are not uncommon in severe cases. Gangrene of the skin is another possibility, especially of that covering the fingers, toes, and ears, and the revolting deformity of the nose endured by Charles IX, of France, was a result of this complication.

Convulsions, delirium, coma, meningitis, or various psychoses afflict some patients. Finally, in this list of horrors, the cornea may become inflamed, with opacity and dimness or loss of vision as a result; or, if the cornea should perforate because of ulceration, infection and total destruction of one or both eyes. This complicating keratitis was one of the most frequent causes of lost vision in prevaccination days, and at one time three quarters of the inmates of an English institution for the indigent blind had been deprived of their sight by smallpox.[1]

The affliction of this awful disease was not suffered with resignation; such is not the nature of mankind. It was noticed centuries ago that a person rarely had smallpox a second time and endeavors were made accordingly to guard against a severe attack, acquired in the natural way, by artificially inducing a milder form. The region and the period in which these early attempts were made are entirely unknown, however, and all that can be said is that preventive inoculation is a practice of great antiquity, and that it came from the people. Writing of it in 1721, de Castro remarked: "That it first proceeded from some of the populace who were neither men of Fortune, Character, nor Learning, seems to me very probable, in that it appeared in the World with-

out the least recommendation from any of the Learned, and met with very considerable opposition from the rich."

Some believe that preventive inoculation originated in Africa, whereas others suggest that it first came into use in the countries about the Caspian Sea and that the Circassians employed it to preserve the beauty of young girls who were destined to be sold as slaves.[4] An eyewitness who saw the operation performed in 1711 on a little Circassian girl by an old woman, as was the usual custom, wrote that after having been purged with dried fruit she was carried to a boy about three years old who had acquired smallpox in the natural way. Several light wounds were made with three needles fastened together, and into them was rubbed matter from the pustules on the boy. After the scarifications had been dressed with leaves and lambskin the little patient was carried home by her mother, and it was expected that she would recover in five or six days.

The technique varied somewhat in different countries. In Greece the scratches were made on the forehead, both arms, and the chest to represent the Sign of the Cross. In Italy, where the people had practiced inoculation for centuries in secret because it was opposed by the upper classes, nurses used to rub the variolous matter into the palms of children entrusted to their care and often without the knowledge of their parents. The Chinese introduced dried pustules into a nostril, the left in boys and the right in girls, a method so different from that employed in other countries as to lead to the belief that it must have been native in origin.

Kennedy, an English surgeon, wrote in 1715 that the Persians took the dried pus internally, whereas the Turks inoculated with fresh matter and at several sites. They selected a "fresh and kindly Pock," by which Kennedy meant one that had not yet become infected, rubbed the pus into several light incisions on the forehead, wrists, and legs, and applied a dressing for a few hours. After eight or ten days "the usual symptoms begin to appear, and the distemper comes forward as if naturally . . . though in a more kindly manner and not near the number of *Pox*." He disclaimed any intention of persuading the English to adopt the custom, even while insisting that the inoculated disease was an

efficient preventive and no more to be feared than the itch. He had been told that of two thousand persons inoculated shortly before in Constantinople not more than two had died in consequence, and death was ascribed to their having carelessly gone out instead of remaining in close confinement at home according to the invariable procedure. The open air had "struck the distemper . . . more inwardly, and was the occasion of their death."

Having noticed that in years when smallpox was especially virulent those who were inoculated had more severe symptoms, the Turks gathered their variolous material from patients with a mild form of the disease, as did the Georgians and the Arabs. But it was in India, where variolation had been practiced from time immemorial, that it reached the highest of its preliminary stages. The virus was taken from a person with inoculated, not natural, smallpox, and was further attenuated by being kept in the dry state for a year before it was used. The method of scarification was better, too, in that the wounds were more superficial and barely deep enough to draw blood, an approximation to the technique employed today.

It was the enthusiasm of Lady Mary Wortley Montagu coupled with her beauty, her wit, and her high social position that was mainly responsible for the introduction of preventive smallpox inoculation into England. Eldest daughter of Evelyn Pierrepont, afterward Earl of Kingston, she was famous for her letters, which were said to have been second only to those of Madame de Sévigné, an opinion that she herself shared: ". . . I assert without the least vanity that mine will be fully as entertaining forty years hence."

A few years after her marriage she accompanied her husband, Edward Wortley Montagu, to Constantinople, where he had been appointed Ambassador. On April 1, 1717, Old Style, she wrote from there to her friend Miss Sarah Chiswell, in part as follows:

A propos of distempers, I am going to tell you a thing that I am sure will make you wish yourself here. The small-pox, so fatal, and so general amongst us, is here entirely harmless by the invention of

ingrafting, which is the term they give it. There is a set of old women who make it their business to perform the operation every autumn, in the month of September, when the great heat is abated. People send to one another to know if any of their family has a mind to have the small-pox: they make parties for this purpose, and when they are met (commonly fifteen or sixteen together), the old woman comes with a nut-shell full of the matter of the best sort of small-pox, and asks what veins you please to have opened. She immediately rips open that you offer to her with a large needle (which gives you no more pain than a common scratch), and puts into the vein as much venom as can lie upon the head of her needle, and after binds up the little wound with a hollow bit of shell; and in this manner opens four or five veins. The Grecians have commonly the superstition of opening one in the middle of the forehead, in each arm, and on the breast, to mark the sign of the cross; but this has a very ill effect, all these wounds leaving little scars, and is not done by those that are not superstitious, who choose to have them in the legs, or that part of the arm that is concealed. The children or young patients play together all the rest of the day, and are in perfect health to the eighth. Then the fever begins to seize them, and they keep their beds two days, very seldom three. They have very rarely above twenty or thirty [pocks] in their faces, which never mark; and in eight days' time they are as well as before their illness. Where they are wounded, there remain running sores during the distemper, which I don't doubt is a great relief to it. Every year thousands undergo this operation: and the French embassador says pleasantly, that they take the small-pox here by way of diversion, as they take the waters in other countries. There is no example of any one that has died in it; and you may believe I am very well satisfied of the safety of the experiment, since I intend to try it on my dear little son.

I am patriot enough to take pains to bring this useful invention into fashion in England; and I should not fail to write to some of our doctors very particularly about it, if I knew any one of them that I thought had virtue enough to destroy such a considerable branch of their revenue for the good of mankind. . . .

Hardly fair, this, toward a profession that has lost so many of its members from infectious diseases acquired while fighting them!

Lady Mary had every reason to fear smallpox, for it had

carried off a nephew and her only brother, and had attacked her so viciously, in or before the year 1715, that during her recovery she feared total disfigurement. This she was spared, but the disease did deprive her of very fine eyelashes and thus gave her eyes a fierceness that impaired their former beauty.

The friend to whom her letter came died of smallpox about nine years later, and the "dear little son" grew up to be a rake who pursued his career of profligacy and wickedness to the end, embittering his mother's heart and shortening his father's days.

Lady Mary and her husband returned from the East in 1718, and when their son subsequently absconded from school the scar from his inoculation helped to identify him. He was described in an advertisement offering £20 reward "and reasonable charges," as having "two marks by which he is easily known—viz. on the back of each arm, about two or three inches above the wrist, a small roundish scar, less than a silver penny, like a large mark of the small-pox."

The popularization of "ingrafting" was a thankless task, which brought this courageous woman nothing but calumny and abuse. In a series of "Introductory Anecdotes" to Lady Mary's *Letters* her granddaughter, Lady Louisa Stuart, wrote:

> Lady Mary protested that in four or five years immediately succeeding her arrival at home, she seldom passed a day without repenting of her patriotic undertaking; and she vowed that she never would have attempted it if she had foreseen the vexation, the persecution, and even the obloquy it brought upon her. The clamours raised against the practice, and of course against her, were beyond belief. The faculty all rose in arms to a man, foretelling failure and the most disastrous consequences; the clergy descanted from their pulpits on the impiety of thus seeking to take events out of the hand of Providence; the common people were taught to hoot at her as an unnatural mother, who had risked the lives of her own children.

"Children" because a daughter was inoculated in England.

Lady Louisa continued: ". . . the four great physicians deputed by government to watch the progress of her daughter's inoculation, betrayed not only such incredulity as to its success, but such an unwillingness to have it succeed, such an evident

spirit of rancour and malignity, that she never cared to leave the child alone with them one second, lest it should in some secret way suffer from their interference."

But in addition to being highly talented Lady Mary, it must be confessed, was somewhat eccentric, and it may very well be that her suspicions here were groundless.

The reader may ask why children were so often mentioned in the early accounts of preventive inoculation. Were they the innocent and helpless victims of experiment? Far from it. They were the beneficiaries of experiment, for smallpox used to be characteristically a disease of childhood, and if it spares children now it is only because they have been so recently vaccinated. They were inoculated with smallpox in the frantic hope of preserving them from the ravages of the disease acquired in the natural way.

Despite all opposition variolation slowly made its way in England, and toward 1760 the technique was vastly improved by Robert Sutton, a man of no medical education. He and his sons, Robert and Daniel, opened a house at Ingatestone, Essex, to which applicants flocked in such number that it soon became difficult to find accommodation for them in the village. According to their own account the Suttons inoculated some seventeen thousand persons, with only five or six deaths. Though regarded by most physicians of his day as a dangerous quack, Sutton devised the best and safest method known until then, one more or less resembling our modern technique of vaccination. His success was due to the use of a minimal amount of virus, taken from a vesicle rather than a pustule and hence free of contaminating bacteria, no less than to a relatively superficial inoculation, which diminished again the chances of secondary infection. In the days before surgical cleanliness was practiced the entrance of harmful bacteria must have been responsible for some of the deaths attributed to variolation itself, though of course this could not be known at the time.[3]

The procedure, which came to be known as Suttonian inoculation to distinguish it from Jennerian vaccination, its one-time rival and ultimate successor, was adopted by Dimsdale, a London practitioner who was so outstanding in his profession that he

was sent for to inoculate Catherine the Great, of Russia. Perhaps in apology for having become the disciple of an irregular practitioner he wrote: "Knowing that improvements which would do honour to the most elevated human understanding are sometimes stumbled upon by men of more confined abilities; and that in medicine, as well as in every other circumstance in life, it is our duty to avail ourselves as much as possible, of all discoveries tending to the common benefit, I embraced every *just opportunity* of informing myself of facts, circumstances, and events, that either public fame, or more precise relations brought me."

In America Cotton Mather played the role of Lady Mary Wortley Montagu and, like her, aroused bitter antagonism.[12] In 1721 he read the account of variolation as it was practiced in Turkey and spoke of it to several physicians but they, well acquainted with his medical whims, paid no attention. Only one listened—Dr. Zabdiel Boylston, of Boston, who, on June 27 of that year, successfully inoculated his only son, six years of age, the first person ever to be submitted to this procedure in the New World. The practice was fiercely resisted. Boylston was mobbed and Mather had a hand grenade thrown in at the window of his home, but Benjamin Franklin, Dr. Benjamin Rush, and many of the New England clergy had the courage to defend it; in consequence of this authoritative support it was gradually extended, and did much to suppress smallpox.

During the early part of the eighteenth century one out of every fourteen uninoculated children died of variola, but only one in ninety-nine among the protected,[19] and in adults the outcome was equally gratifying. By the end of 1776, for example, smallpox had seriously impaired the strength of Washington's army, and fear of it had almost stopped the flow of recruits.[23] He had written to Patrick Henry, according to Thursfield, that the disease was more destructive to an army than the sword; so, convinced of its necessity, he determined on wholesale inoculation. Congress passed the necessary measure, and within a few weeks his army was free of smallpox. Its great commander did not share the general experience, however, for he had already passed through the disease,[21] as all his portraits would show if the artists

had not been too considerate or too tactful to reproduce the pitting.

Variolation had some grave disadvantages in spite of all its merit. There was the ever-present danger of wound infection already alluded to, but much more serious was the fact that the inoculated person had real smallpox, and though it was usually of the mild sort a mortality of from 1 to 3 per cent was common, and one of 12 per cent not unknown. Again, the inoculated disease could be transmitted to others as readily as smallpox contracted in the natural way, sometimes assuming a virulent form in these instances; such was the case when an inoculated child gave variola to seventeen persons, of whom eight died.[10] The individual was protected but the community was endangered. Add to these disadvantages the additional one that variolation sometimes gave with one hand and took away with the other, conferring resistance to smallpox and transmitting syphilis at the same time, and it will be clear why it was abandoned as soon as a safe substitute had been found. Yet Dr. Milton J. Rosenau learned that it was still practiced in central Africa in 1922, and had himself witnessed it in an Arabian village in Palestine.

How did it feel to be inoculated against smallpox? Fortunately Peter Thacher, twelve years old, recorded his experience in a diary and it has been given to the world by Dr. Reginald Fitz, of Boston.

"Boston, Saturday, April 14, 1764. I was inoculated at the George Tavern by Doct. Joseph Gardiner." According to the established ritual Peter spent most of the following weeks taking laxatives, which on some days operated as many as nine times. On the 21st the powder "worked me 4 Times down and once up. . . ." On the morning of this day he felt very ill, marvelous to relate, and did not get up until ten o'clock. "I have some Pock come out to Day."

"Sunday, April 22. Felt charmingly all day. I had more Pock come out to Day. At night took Brimstone in Milk for a sore Mouth."

On Monday, the 30th, he went downstairs, his sore throat

well, though it had afflicted him "much," and his pustules drying up. The account ends:

"Thus, through the Mercy of God, I have been preserved through the Distemper of the Small Pox, which formally was so fatal to many Thousands. The Distemper is very mortal the natural Way. I should have a thankful Heart for so great a Favor. I confess I was undeserving of it. Many and heinous have been my Sins but I hope they will be washed away."

Young Master Thacher was graduated later from Harvard College, and it is consoling to learn that he became a fluent preacher and, as Fitz assures us, amply atoned for the many and grievous sins of his extreme youth.

There is an epidemic eruptive disease of the cow called vaccinia, or cowpox, caused by a virus that is closely related to, and is probably a modification of, the virus of smallpox. Spread through a herd by the hands of milkers, it appears on the udders and teats as small red papules, which are soon converted into vesicles and ultimately into pustules that break and discharge their contents. Though attended by some rise of temperature it is followed by no serious consequences, and is generally regarded by dairymen as of but little import. It is not so frequently seen in England now as in earlier years, but is far from uncommon in the United States.[11] Where the virus hides between epidemics is an unsolved problem, nor is it known how it reaches new herds to cause an outbreak.

Those milking affected cows often contract the disease, small wounds on the hands furnishing a convenient portal of entry for infectious material from the running sores. From five to seven days after contact "milker's nodules," small, hard, usually painless, and bluish-red papules, make their appearance and advance within a few days through the stages of vesiculation and pustulation; not infrequently there are similar lesions on the wrists and forearms where they rub against the udder, and still others sometimes break out on the lips, nose, eyelids, or other parts of the body that have been rubbed or scratched by the infected fin-

gers; there may be as many as forty. Usually there is some slight fever with chilly sensations, pain in the limbs, and headache, all of which passes away within a few days. The nodules themselves heal in from four to six weeks, generally without scarring.

In various parts of the world, but particularly in Gloucestershire, Dorsetshire, Derbyshire, and other English dairy counties there had long been a tradition that those who had acquired cowpox enjoyed immunity from smallpox. What more natural, then, than that an attempt should be made by the country folk to communicate cowpox by intent, and so reap the benefits resulting when the disease was contracted in the natural way?

"A very respectable practitioner," wrote Crookshank in his history of vaccination, reported that among seven children he had inoculated with smallpox, five had been purposely infected with cowpox by being made to handle the teats and udders of infected cows. The resulting cowpox had made them resistant to his inoculation with smallpox, whereas the other two children were successfully variolated. Robert Fooks, a butcher near Bridport, was deliberately infected with cowpox in 1740 at several sites on the hands with a needle, and four subsequent attempts with smallpox, the last two a considerable time after his infection with vaccinia, were all failures. In 1782 Mrs. Rendall, the wife of a farmer, vaccinated herself and three or four children with cowpox, and at about the same time the Rev. Herman Drew was recommending and practicing the procedure. In Ireland an eighty-year-old woman said about 1750 that as long as she could remember the opinion had prevailed that those who had had cowpox could not get smallpox, and that people therefore exposed themselves purposely to the former.

But the most famous of the early vaccinators was Benjamin Jesty, a prosperous farmer of Dorsetshire. In 1774 smallpox had attacked his community, and he was alarmed for the safety of his family; not for his own, since he had previously contracted vaccinia in the customary way. The fact that two of his maidservants, Ann Notley and Mary Read, who had previously had this disorder had attended relatives suffering from smallpox without themselves being infected made him endeavor to pro-

tect his wife and two sons, Robert and Benjamin, three and two years old respectively. He took them all to a farm near his own where cowpox had broken out, and introduced the virus into their arms with a needle. The boys had mild attacks in consequence but Mrs. Jesty nearly lost her arm and, indeed, her life. Mr. Read, a neighboring surgeon called in to attend her, said to Jesty: "You have done a bold thing, but I will get you through it if I can." He was as good as his word for she soon recovered perfectly, but the audacity of the attempt and the threatening consequences caused alarm in the family and a small sensation in the neighborhood, and Jesty never repeated the operation.

Fifteen years later the sons were inoculated with smallpox by Mr. Trowbridge, together with others who had not had cowpox. The Jestys were resistant, whereas the others went through the usual course of inoculated smallpox.

Dr. George M. Gould said of Jesty's work:

I cannot forbear admitting that this magnificent act of Jesty has never been rated at its true value. That Jesty was a layman does not detract from the honor that is his due, but, to my mind, adds to it. Neither Jesty nor Jenner discovered the fact of immunity from vaccinia, and neither could explain it. That Jenner waited twenty-five or thirty years after the dairy folk had found the truth, and twenty-two years after Jesty vaccinated his family, before he vaccinated the Phipps boy, is not a reason for making Jenner the discoverer of vaccination. That honor seems to me to be due to Benjamin Jesty.

Edward Jenner, who developed the technique of vaccination and in so doing converted a rural tradition into an established fact, was born at Berkeley, Gloucestershire, on May 17, 1749, into a prominent family, the third son of the Rev. Stephen Jenner.[1] His mother was the daughter of the Rev. Henry Head and two of his brothers were clergymen, so he must have escaped the Church by a narrow margin.

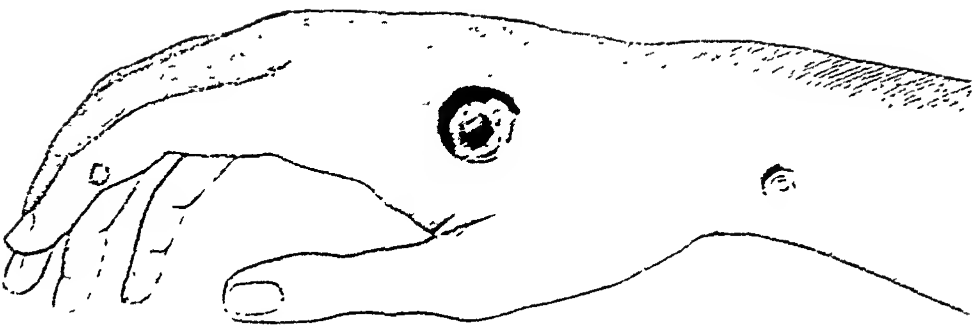
After having finished his elementary schooling he was apprenticed, at the age of thirteen, to Mr. Ludlow, an eminent surgeon of Sodbury, to be instructed in the elements of surgery and pharmacology. During his term there a young countrywoman

came to seek advice, and upon the subject of smallpox being mentioned she remarked: "I cannot take that disease, for I have had cowpox." The statement excited Jenner's interest, for it was the first time that this widespread idea had been so forcibly brought home to him. The impression then made never left him and he dwelt constantly on the matter—so constantly, according to Baron, his friend, medical attendant, and biographer, that his colleagues came to look on him as a nuisance and threatened to expel him from a small medical society of the neighborhood if he continued to harass them.

The physicians with whom he discussed the question knew of instances that corroborated the popular belief in the protective virtues of vaccinia, but they knew also of persons who had had cowpox yet nevertheless had subsequently contracted smallpox. Hence they regarded the notion as a vague rumor from which no information of value could be gathered, attributing the supposed protective power to some constitutional peculiarity in the person who escaped smallpox rather than to any special virtue on the part of vaccinia.

In his twenty-first year Jenner went up to London to continue his education under the great physiologist and surgeon, John Hunter, in whose family he resided as a favorite pupil for two years. Returning to Berkeley at the end of this period, he began the practice of his profession. In March, 1788, he married a Miss Kingscote, an understanding and accomplished girl, whose first name provides an admirable example of the handicaps under which historians must suffer, for it appears variously as Catharine, Catherine, and Kathleen. Unless it be a misprint the first version seems most likely the correct one, since it is that given by Baron. In 1792 Jenner was awarded the degree of M.D. by St. Andrews.

The doctor was of somewhat less than medium height, well formed, and active. He was good-natured, modest, an amusing conversationalist, unusually neat in his dress, fond of literature and especially of natural history, had a rather good voice, and played the flute as well as any accomplished amateur. His friend Edward Gardner said that in becoming a physician he had lost



THE HAND OF SARAH NELMES

the opportunity of acquiring renown as a poet, but this was the indulgent opinion of a friend rather than the impartial judgment of a critic. With the exception of one or two his poems hardly rise to the level of mediocrity and some, like the following, are but mildly amusing doggerel.

ON THE DEATH OF AN OLD WOMAN NAMED HEYWOOD, NOT REMARKABLE FOR HAVING LED AN EXEMPLARY LIFE

Tho' some may exclaim 'Twas strange, or 'twas cruel,
Yet 'tis said to be true; Old Nick wanting fuel,
Gave an order for faggots well-season'd and good;
So Death took his hatchet and cut down Hey—wood.

His vocation together with his numerous hobbies left no time for what had once been an obsession, and it was not until 1775 that he was able to begin an examination of the tradition respecting cowpox. The work went slowly, however, because it was interrupted several times by the disappearance of cowpox from the dairies and once by a long illness that nearly cost him his life.

It turned out ultimately that many kinds of eruption affected the udders of cows, a few of which were communicable to the hands of milkers, and that any sore thus produced was called cowpox by the dairy people. But only vaccinia had the power to immunize against smallpox, so Jenner called all the other diseases spurious cowpox in order to distinguish them from the true variety. Next he was disappointed to find that smallpox could occur even in persons who had had true cowpox, but this was explained when he discovered that the virus of cowpox varied in its immunizing power.

So, with one interruption and disappointment after another, he went patiently on, and something over twenty years elapsed before he performed his first vaccination. In May, 1796, cowpox broke out again and Sarah Nelmes, a dairymaid, was infected on a hand that had been scratched by a thorn. On the 14th of the month he successfully infected the eight-year-old James Phipps with matter taken from the girl and inserted into the arm of the

child through two superficial incisions, each about half an inch long and barely penetrating the outer skin.

"On the seventh day," wrote Jenner, "he complained of uneasiness in the axilla, and on the ninth he became a little chilly, lost his appetite, and had a slight head-ache. During the whole of this day he was perceptibly indisposed, and he spent the night with some degree of restlessness, but on the day following he was perfectly well." [22]

About six weeks later Jenner inoculated the little lad with fresh smallpox material in order to see whether he had been made resistant, and the test was repeated several months afterward but no sensible effect was produced on either occasion.

About the end of June, 1798, there appeared what has since become one of the great classics of medicine; a small quarto volume of some seventy pages entitled: *An Inquiry into the Causes and Effects of the* VARIOLAE VACCINAE, *a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire and Known by the Name of the Cow Pox.*

Though some of his professional brethren accepted Jenner's results gladly others did not and, together with the laity, strongly opposed vaccination. In addition to doubts regarding its efficacy there was considerable jealousy and attempts were made to appropriate part of the credit, to belittle the work, or to question its originality. It was said that others had performed vaccination before him, as, in fact, they had, and that in any case it had no advantage over inoculation with smallpox. The fantastic idea was advanced that vaccination would cause the human subject to sprout horns, low like a cow, and acquire other bovine characteristics.[19] Finally, it was asserted that medicine had merely introduced one more disease into the human system before learning to cure those already known.[8]

On the other side of the ledger there were the honors heaped upon Jenner as the passing years showed the incalculable worth of vaccination. These included two Parliamentary grants amounting to £30,000 in all, which did little more than pay the expenses of his investigation. England, says Dr. H. W. Haggard, lavished millions in money and freely bestowed honors, peerages,

and heavy annual pensions upon the soldiers who were most successful in fighting her battles and destroying their fellow men. She grudgingly rewarded Jenner with £30,000 for preserving thirty thousand of her subjects yearly; yet his lancet saved far more human lives than the sword of Napoleon destroyed.

In addition to this inadequate grant there was a public subscription from India that brought in something over £7,000; an honorary degree from Oxford; various addresses and testimonial letters; and, most touching of all, a belt and a string of wampum from a tribe of American Indians "In token of our acceptance of your precious gift, and we beseech the great spirit to take care of you in this world, and in the land of spirits." [12]

Springing years later to Jenner's defense, Captain Roddis said that Jenner had freely admitted his knowledge of the belief in the protective virtues of cowpox, and that he probably knew nothing of Jesty's work. His claim to distinction rested on the fact that he took a countryside tradition derided by other members of his profession, studied it for more than twenty years, observed, experimented, recorded his findings, bore up under numerous disappointments, and overcame many difficulties.

Because of the dispute over priority Jesty was asked to London but fearing an attack of gout, to which he was subject, declined the invitation.[4] In the course of the next year, when the Parliamentary grant to Jenner was under consideration, there was a second request, in which Jesty was promised that he would be given 15 guineas to cover his expenses, would not be asked to stay longer than five days unless he so desired, and would have his portrait painted as the earliest vaccinator.

This time he did accept, taking with him his son, Robert. Jesty attracted great attention from members of the Jennerian Society, who were highly amused by his appearance and his peculiarly old-fashioned suit; for although his family had urged him to buy new clothes in which to meet all the great folk in London he had refused, asking why he should dress better in town than in the country. To prove their good faith Robert Jesty willingly consented to be inoculated with smallpox and his father to be vaccinated with cowpox, but neither disease took ef-

fect. Jesty was presented with a pair of handsome gold-mounted lancets and his portrait was painted by Sharpe, though he was such an impatient subject that he could be kept quiet only by having Mrs. Sharpe play to him on the harpsichord.

Jesty felt that he, equally with Jenner, was entitled to some reward and brought with him a letter from his rector, the Rev. Andrew Bell, to whom he had described his procedure. Although Dr. Bell had written it according to request, he had expressed the fear that Jesty was too late in advancing his claim, as he had not made his discovery known at the time and had vaccinated only members of his own family. After having adduced the evidence as desired Dr. Bell ended his letter of August 1, 1803, with the following words:

With those who objected to introducing the bestial disorder into the human frame, already liable to so many diseases, the farmer has been heard to say that he argued after this manner:—

For his part he preferred taking infection from an innocent animal like a cow, subject to so few disorders, to taking it from the human body, liable to so many and such diseases; and that he had experience on his side, as the casual Cow Pox was not attended with danger like the variolous infection; and that beside, there appeared little risk in introducing into the human constitution matter from the cow, as we already without danger eat the flesh and blood, drink the milk, and cover ourselves with the skin of this innocuous animal.

Upon his return from London Jesty gave a highly unfavorable account of the metropolis, though he admitted to one great comfort there: He could be shaved every day rather than once a week as at home, when on Saturdays he rode in to Wareham market for the purpose.

Jesty does not seem to have pressed for any pecuniary reward during his sojourn in London, but in the following year he wrote to Dr. George Pearson, a member of the Jennerian Society, on the matter. His letter was communicated to the members of the Vaccine Institution, whose secretary replied that he would endeavor to advance his interest but feared it was highly improbable that any award would be made. After this Jesty gave up all

expectation, and his circumstances were such as to make the question of little import to him.

He died in 1816, at the age of seventy-nine, and lies buried in the little village of Worth Matravers, near Swanage, from which Downshay, his farm, was not far distant.[19]

SACRED
To the Memory
of
BENJN. JESTY (of Downshay)
Who departed this life
April 16, 1816
Aged 79 years

> He was born at Yetminster in this County, and was an upright Honest man; particularly noted for having been the first person (known) that introduced the Cow Pox by inoculation, and who, from his great strength of mind, made the experiment from the Cow on his wife and two sons in the year 1774.

Jenner survived him by seven years, dying at the age of seventy-four on Sunday, January 26, 1823, of a massive cerebral hemorrhage suffered on the preceding day. He was buried in the churchyard that adjoined his home in Berkeley.

There is a close parallel between Edward Jenner and William Withering, the advocate of foxglove. Both were born in southwest England, the former in 1749, the latter in 1741, and passed their lives as country doctors there. Both were fond of literature, music, and natural history. Their books, two of the great classics of English medicine and small volumes both, were published only thirteen years apart. Both men had the sagacity to see the immeasurable value of what others regarded as old wive's tales, and both lived to see the stone that the builders rejected become, through their own efforts, the head of the corner.

With the passage of the years the preparation of vaccine virus has naturally undergone improvements. For a long time the calf has been used as a source, partly because it is more easily handled than grown animals, partly because its delicate skin gives rise

to a larger vesicle and therefore provides more material, and partly because it is milk fed and its stall accordingly free from dust and all the chances for contamination that dust would entail. The seed virus with which it is vaccinated may be that of natural cowpox, or the virus of smallpox attenuated by successive passage through calves. If this process be continued too long, however, the virus loses strength and its activity has to be restored by passage through another species, often the rabbit.

In spite of the greatest care bovine virus is always contaminated with bacteria, which by good fortune as well as by good management are almost invariably harmless and can be killed off by storing the preparation in glycerol for a time. Its production is under the strictest government control and, needless to say, none is ever used until its bacterial content has been determined and found so small and of such nature as not to constitute a hazard.

Nevertheless, the pre-eminence of the calf has been seriously threatened of late by the hen's egg, in which virus can be grown under perfectly sterile conditions; an added advantage of virus thus cultivated is that it elicits a milder reaction in the patient than does the bovine variety, though even the latter causes but little trouble.

The technique of vaccination, too, has been improved. Dried virus on a thread, quill, or other vehicle has been replaced by a fluid preparation contained in a capillary tube, and incisions and scratches have given way to the multiple pressure method. A drop of vaccine is expelled on the skin, preferably of the arm, and the point of a needle that is held almost parallel with its surface is pressed through the drop and just barely into the skin about thirty times, within an area not much larger than one eighth of an inch in diameter. As the point of the needle is lifted each time a few of the surface cells are torn away, providing a sufficient portal of entry for the virus. In no case must blood be drawn or the scarfskin gone through.

Three days later a papule appears at the site in a successful case, by the sixth day this has changed to a vesicle, and by the ninth to a pustule. Constitutional symptoms make their appear-

ance about the seventh day—slight headache, muscular pains, loss of appetite, and other accompaniments of a mild fever. These vanish within a few days, leaving behind them an immunity to smallpox that may be depended upon for some years, the period varying from person to person. Authorities advise that children be vaccinated at the age of six to twelve months and once more when about six years old, and that revaccination be performed again between fifteen and twenty. In the presence of an epidemic, of course, revaccination is imperative, and after contact with a smallpox patient mandatory in any enlightened community.

A small price indeed for insurance against one of the most devastating of all the acute infectious diseases!

VI

THE LARYNGEAL MIRROR

"Say 'a-a-ah,' please." The little round mirror that presses against the back of your throat as an accompaniment to this gentle command, warmed to prevent fogging by the breath, was adapted to its purpose by a Spanish singing teacher. Adapted, look you; not invented, as some seem to think, since mirrors for examining the various cavities of the body had already been in use for some two hundred years.

The nose, the ear, and all the other body apertures had been accessible for centuries to inspection; so accessible, indeed, that amazement has been expressed at the knowledge and skill displayed by the physicians of an age now long since vanished. Specula to dilate and survey the various canals opening on the surface of the body have been unearthed in the ruins of Pompeii, which was destroyed in the year 79 A.D.; they were employed in India, too, and are mentioned in the Talmud.[0] The sun served everywhere as an illuminant until the thirteenth century, when candlelight was proposed as a substitute, and a book published in Venice as early as 1587 suggested concentrating its rays by means of a globular flask filled with pure water; this, of course, was nothing less than a lens.

Toward the middle of the seventeenth century Borell, a physician of Paris, introduced a concave mirror, over whose edge he used to peer since it had no central perforation as have ours of today; in this he studied reflections of the nasal cavities and other orifices, casting light into them with a second concave mirror, and said that he could see more than ever he had been able to see with a speculum. The next advance came in 1789, when Archibald Cleland, an English army surgeon, described an apparatus bearing a candle, and in front of it a biconvex lens to "dart the collected Rays of Light into the Bottom of the Ear,

or to the Bottom of any Cavity that can be brought into a strait Line." This was given a more elegant form some thirty years later by Arnaud, who incorporated it in a lantern much like the old-fashioned dark lantern, or thieves' lantern, as the Germans call it, which he employed to illuminate orifices that he wanted to examine. Thus he was the author of the first endoscopic lamp.

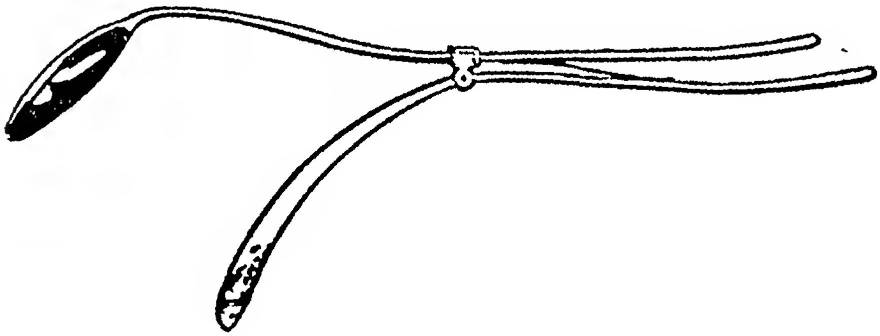
Reflected light, as distinguished from the direct light that had been used until then, was introduced about 1743 by Levret, of Paris, who achieved better illumination of a cavity by inserting a mirror of polished steel, to aid him in placing ligatures around nasal polyps that he was about to remove by constriction.

Though none of these men appear to have been bold enough to venture upon inspection of the larynx, it is clearly apparent that endoscopy, or the examination of hollow organs, was a well-established procedure long before 1805. In that year Bozzini, of Frankfort-on-the-Main, usually regarded as the pioneer, began his attempts to examine the various apertures of the body, the larynx among them. An absurd idea prevailed that he proposed to inspect not only these but the internal organs as well, so his confreres either laughed in their sleeves or frowned openly on his assumed pretensions, calling his instrument "a magic lantern in the human body." [6] It consisted of a tin lantern, shaped like a vase and bearing a small wax candle, together with a number of metal tubes for insertion into the different cavities. The laryngeal tube was equipped at its downward bend with two mirrors; one to reflect the light, the other to receive the image, for Bozzini did not realize that one would have served both purposes. This formidable contrivance was about thirteen inches long and correspondingly wide, and nothing of value emerged from its use, as may well be imagined, either to the patients or to the art of medicine.[1] The exact dimensions of today's laryngeal mirror cannot well be given for comparison with Bozzini's unwieldy apparatus, since the modern instrument comes in more than half a dozen sizes. This much, however, can be said; it duplicates in shape the all too familiar dental mirror and is not more than seven eighths of an inch in diameter, with an adjustable handle about seven inches in length.

The next candidate for fame was a French physiologist, Cagniard de la Tour, who conceived in 1825 the idea of employing a mirror, which he introduced into his own throat, hoping with solar rays and a second mirror to see the glottis. Meeting with partial success at the most, he was discouraged from any further effort.[16]

Two years later Louis S. Senn, a physician of Geneva, fastened a small mirror to the end of a thin wire in an endeavor to reveal the cause of hoarseness and painful swallowing in a little girl of seven. Though he used no illumination, and disappointment inevitably followed, he gained the impression that the experiment might succeed in grown persons, ascribing his failure to the dimensions of the mirror.[8]

It was two years after this that Benjamin Guy Babington, a Scotsman, demonstrated before the Hunterian Society of London his "glottiscope," an oblong mirror set in silver wire and borne



Babington's Glottiscope

on a long shank, and thus not wholly unlike our modern laryngeal mirror.[14] Upon this he directed the sun's rays with a common hand looking glass. The patient sat with his back to the sun, and while the looking glass was held in the left hand of the observer the laryngeal mirror was introduced into the throat with his right. A simple attachment to the shank of the latter depressed the tongue, an unruly member in more ways than one that hitherto had offered the chief obstacle to inspection of the larynx; nowadays the head mirror or head light leaves one of the physician's hands free to cope with it. Babington's instrument

could not have been an unqualified success, for he finally abandoned his combination mirror and tongue depressor and took to a mirror somewhat resembling those now in use. Though the method was a decided advance over that of Senn, who cast no light upon his laryngeal mirror, and though Babington tried the glottiscope on many patients, he left no record of his results. It had two obvious disadvantages: it demanded the use of both the observer's hands; and sunlight is not always available, certainly not in the British Isles.

Bennati, of Paris, asserted in 1832 that he could see the vocal cords.[16] "A very ingenious mechanic" named Selligue had invented a laryngoscope with two tubes, one to carry light into the glottis, the other to send back its image from a mirror in the end of the second tube. But Trousseau, the great French clinician, who had ordered one for his own use, insisted that Bennati could not possibly have seen the larynx because the apparatus set up so much gagging, with consequent closure of the throat, that the larynx would have been concealed from view. And indeed the instrument was so difficult to use that it was said only one patient in ten could tolerate it.[6]

A mirror described as about the size of a two-franc piece, or something smaller than our half dollar, was presented in 1838 before a medical society in Lyons by Baumès, who left no written description of its use though asserting that it was of great value for examining the larynx.[6]

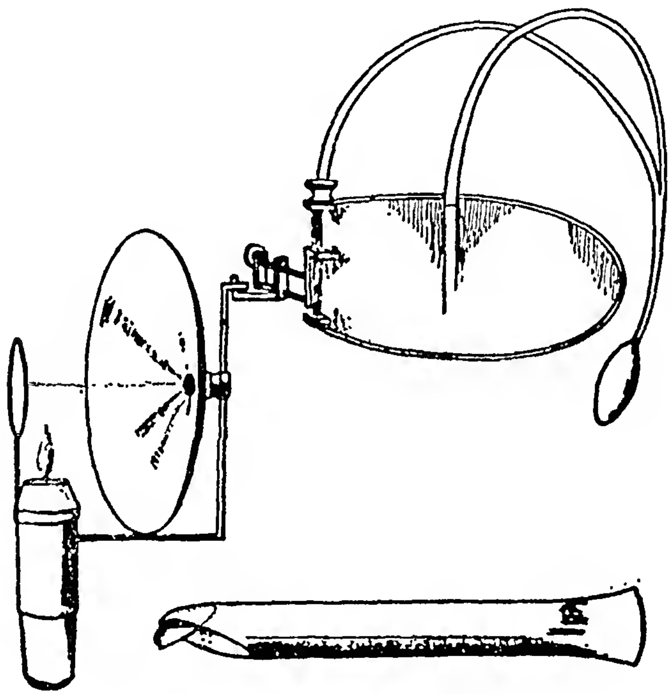
Efforts were made two years later by Liston, a Scottish surgeon, to obtain a view of the larynx "by means of such a glass as is used by dentists, on a long stalk, previously dipped in hot water," and carried well back into the throat. Whereas much credit has been accorded him, he examined only swellings that obstructed the laryngeal orifice and made no attempt to see the vocal cords.[6]

Four years passed by and Warden, of Edinburgh, reported two cases in which he had been able to see the glottis by means of a tube and two prisms; one for throwing lamplight into the tube and the other, placed at its lower end, to cast the light down upon the glottis. To facilitate the examination, which the patients evidently found rather strenuous, he advised quieting the irritability

of the throat by touching it with the finger, depressing the tongue, and dilating the back of the throat, meanwhile encouraging the patient to swallow in order to raise the larynx.[6]

Well, the Scots are a hardy race, but this was too much even for them and the method soon languished and died. It might have fared better had cocaine been available, but the employment of this drug as a local anesthetic was still four decades in the future.

At about the same time Avery, of London, was trying to see the vocal cords with a device somewhat similar to Bozzini's, except that the reflecting mirror was set in a single tube. He used a small lamp attached to a head piece, with a reflector behind it



Avery's Laryngoscope

that was concave and perforated in the center like those of today; but the laryngoscope itself was unwieldy and irritated the throat, the apparatus on the good doctor's head weighed a pound, and altogether both he and the patient must have been about equally uncomfortable.[6]

All these men had been trying to see the vocal cords in order that they might understand and intelligently treat such conditions as hoarseness, loss of voice, and so on, but the problem was finally solved by one who had a wholly different end in view.

Manuel Garcia, a singing teacher of London, was enjoying a well-earned vacation in Paris.

One September day, in 1854, I was strolling in the Palais Royal, preoccupied with the ever-recurring wish so often repressed as unrealizable, when suddenly I saw the two mirrors of the laryngoscope in their respective positions, as if actually present before my eyes. I went straight to Charrière, the surgical-instrument maker, and asking if he happened to possess a small mirror with a long handle, was informed that he had a little dentist's mirror, which had been one of the failures of the London Exhibition of 1851. I bought it for six francs. Having obtained also a hand mirror, I returned home at once, very impatient to begin my experiments. I placed against the uvula the little mirror (which I had heated in warm water and carefully dried); then, flashing upon the surface with a hand mirror a ray of sunlight, I saw at once, to my great joy, the glottis open before me, and so fully exposed, that I could perceive a portion of the trachea. When my excitement had somewhat subsided, I began to examine what was passing before my eyes. The manner in which the glottis silently opened and shut, and moved in the act of phonation, filled me with wonder.[14]

Since the earliest days of his career Garcia had been deeply interested in the conformation of the vocal organs, and the unattainable wish to which he referred was the desire to see "a healthy glottis in the very act of singing." [14] At the age of thirty-five, and some fourteen years prior to his great experience, he had presented before the French Academy of Sciences a paper that earned him the official congratulations of that august body, and laid the foundation for all subsequent investigations on the voice. But he had not yet realized his consuming ambition, nor had anyone else achieved more than a fleeting glimpse of the vocal cords, for by reason of its situation the larynx had offered a peculiarly difficult problem.

Throughout western Europe laryngoscopy was in the air when Garcia first made his attempt. Why should he, a singing teacher, triumph so brilliantly where the physicians of France, of Germany, of Switzerland, and of Great Britain had failed so ignominiously or met with partial success at the most? Before Garcia's time the larynx as a whole had probably never been seen in the living subject; all that had been achieved was isolated and incomplete examination, followed by neither theoretical nor practical advantage and inadequate to convince even the inventors of the various instruments that they possessed any value whatsoever.

The answer is that several factors were concerned in his good fortune. First, he was no mere singing teacher, but a man with a consuming interest in the anatomy and physiology of the larynx; a man who had dissected it on countless occasions and pondered over it day and night, and who was no doubt at least as familiar with it as many a physician of his time. A second reason is that, like de la Tour, he experimented first upon himself and so was able to conduct his manipulations with more delicacy, guided as he was by the sense of touch at both ends of his instrument. But most important of all, perhaps, he had learned as a singer to depress the base of his tongue. He did not draw the organ forward and, indeed, could not have done so because both hands were occupied with his mirrors; thus he failed to see the anterior ends of the vocal cords, and frankly confessed as much. But since most of the movement in singing and speaking takes place at their posterior ends, he saw much more than he missed.

Until he showed the way, the views of anatomists and physiologists on the production of the voice were far from harmonious, for the process was understood only in part by comparison of the larynx with other musical instruments, by fugitive glimpses through accidental wounds, and by experiments on animals. Now, through observation on himself, and on other singers, with whose cooperation he eagerly pursued his investigations, Garcia learned that the vocal cords alone give rise to the voice, and that changes in the position of the parts immediately adjacent to them and variations in the form of the nose and throat merely influence

its timbre.[2] In his *Observations on the Human Voice*, read on May 24, 1855, before the Royal Society of London, he explained that tones are elicited when the stream of expired air is divided into a series of uniformly recurring blasts, which he called explosions, by the regular vibrations of the vocal cords. The closed cords are pushed apart by the escaping air, but because of their elasticity they immediately come together again. When they are in close apposition the tones are pure or, as Garcia said, brilliant; when contact is incomplete the tones are veiled. He then went on to tell how the different registers, chest, falsetto, and head tones, are entirely determined by the shape of the cords and the extent to which they vibrate;[2] and how the "breaking" of a boy's voice as he approaches puberty is due to their elongation, consequent upon a growth of the laryngeal cartilages that produces the prominent "Adam's apple."[10]

None of these things were known until Garcia saw and described them.

His work has been justly appraised as a meritorious exception to the superficial and arbitrary procedures in vogue among most singing masters of his day. Not, it was explained, that one should sing in accordance with physiological precepts, consciously relaxing or contracting such and such a muscle in order to produce this or that tone; but that Garcia was fully justified in emphasizing the anatomy and physiology of the larynx, because a teacher should know how to correct faults.[12]

So far as England was concerned Garcia's discovery shared at first the fate of Babington's, his paper having been received with apathy, if not downright incredulity. He was known to have an unusually tolerant throat, which, as a singer, he was able to keep under perfect control and thus support prolonged contact of the laryngeal mirror without gagging; hence his observations were thought to be of limited applicability at the best. But the fact that he was not a member of the medical profession may have played its part, too, in lessening the interest shown by physicians in his epoch-making discovery.[6]

Attention was drawn to it by a conflict over priority on the Continent.[2, 6]

In 1857 Ludwig Türck, of Vienna, was examining the larynx in the dead and the living subject by means of a small mirror fixed on a long handle, with direct sunlight as an illuminant. Ignorant of previous attempts, he learned of Garcia's discovery only in the summer of that year from the physiologist, Carl Ludwig, to whom he was demonstrating the larynx in some of his patients. As the autumn of 1857 was cloudy in Vienna he laid his experiment aside, to be resumed in the first bright days of spring, apparently with no realization of its full significance.

Johann Nepomuk Czermak, a physiologist of Cracow and later of Budapest, another of those to whom Türck showed the method, borrowed the little mirror that its inventor had cast aside for the moment, in order to study certain guttural sounds such as occur in the Arabic language. He improved the technique by substituting lamplight for the sun's rays and concentrating it with a concave ophthalmoscopic mirror. Because of his capacious throat and his small uvula and tonsils Czermak was a splendid subject for laryngoscopy, and the success of his experiments on himself filled him with delight. Overflowing with enthusiasm, he began a tour of the great European medical centers, demonstrating the method on himself and on anyone else whose consent he was able to gain and exciting, nay, compelling, an interest in what had been abandoned by most physicians as impractical and even derided in some quarters as a mere scientific toy.

There followed a struggle for priority between Türck and Czermak that has been described as a scientific race in which the former was first and the latter a good second.[15] Now beyond question Türck was an independent discoverer of the laryngeal mirror though, like Garcia, he employed sunlight; and whereas Garcia was not in a position to do more than recommend the use of the instrument in treatment, Türck had actually made a few attempts in this direction. On the other hand, Czermak insisted that were it not for his lamp and head mirror laryngoscopy would have been a stillborn child. Faced with the difficulty of deciding to whom priority rightfully belonged, and wholly ignorant of the history of endoscopic examination as it is known today, the commission appointed to look into the matter awarded honorable

mention to both contenders and divided the Montyon Prize equally between them, giving 1,200 francs to each.

The question need not detain us. Enough that Babington was first to demonstrate the possibility of viewing the interior of the larynx; that the earliest successful attempt to see the vocal cords was made by Garcia, and independently by Türck three years later; and that perfection of the technique and realization of its possibilities must be credited to Czermak.

The benefits that followed were greater than even the enthusiastic Czermak had foreseen, and in the days before radiography had reached its modern high precision the little round mirror was often relied upon to give the first warning of disease in organs remote from the larynx. Some say, too, that it was instrumental in the discovery of adenoids, by Wilhelm Meyer, of Copenhagen, but Wright remarks that Meyer was not especially skillful with the laryngeal mirror and discovered them by digital examination. However this may be, the words of F. C. Ewing still hold: "he opened the ears of the deaf . . . he tuned . . . the human voice. . . . And generations to come need not, as now, look upon pictures of the pinched, dull faces of their ancestors, in album and gallery."

Because of Türck's great skill and his prominence as author of an imposing textbook and atlas on diseases of the larynx, Vienna soon became a center for the study of disorders of the upper air passages. Thither flocked students from all parts of the world and thence, in 1858, Horace Green, of New York, first to use the laryngeal mirror in this country, procured his instrument.

Manuel Patricio Rodriguez Garcia was born on March 17, 1805; not in Madrid, as has been so often stated, says M. Sterling Mackinlay, his pupil and biographer, but in Zafra, Catalonia. His mother was Joaquina Sitchex, a well-known dramatic artist of her day. His father, Manuel del Popolo Vincente Garcia, a tenor of renown and trainer of nearly all the greatest singers in the first half of the nineteenth century, had taken Garcia as a stage name and thereafter it remained permanently in the family. The gods were generous in their distribution of talent among the

children of this couple, for in addition to the distinguished son there were two famous daughters: Marie, afterward the celebrated Madame Malibran, born in 1808, who had a soprano voice of unusual beauty and phenomenal compass and, unlike so many singers, dramatic talent to match; and Pauline, born in 1821, who also became an operatic star of the first magnitude. The older sister died at the age of twenty-eight in consequence of a fall from her horse; the younger, as Madame Viardot, lived to be eighty-nine.

After a notable career as singer and composer in Spain, Italy, and France the father crossed to New York in 1825, taking with him an opera company of excellent artists among whom were Manuel and Marie.[6] The tour was extended to Mexico City, where they found upon arriving that nearly all their music had been left behind or lost en route; the elder Garcia thereupon sat down and wrote out the scores of all the operas in their repertoire from memory, giving each one as it was finished to copyists who prepared the separate parts for the various instruments.

But this was only the beginning of a calamitous venture. On their way home after a highly successful season in the Mexican capital the company was set upon near Vera Cruz by brigands, who robbed the impresario of all he possessed and, not content with that, made him sing for their entertainment. He had hoped to found an Italian theater in New York, but the loss of his entire fortune compelled his return to Paris, where he soon retired from the operatic stage and devoted himself exclusively to teaching.

Manuel, the son, studied singing and harmony under various masters in Paris and Madrid and later under his father, without interruption save for the ill-fated trip to Mexico. After his return to Europe, in 1829, he gave up the stage to assist with his father's teaching; for though he had sung with charm as a boy his voice was never powerful, and it is obvious from the verdict of the critics that he never could have become an operatic singer of the first rank. He attributed what he called the ruin of his voice to persistence in training throughout puberty, and held ever afterward that all singing should cease at the very first sign of this transition.

From early youth his tastes had been scientific and he was passionately fond of chemistry, anatomy, and all other subjects that had to do with the human body.[10] Yet one day he was suddenly seized by an ambition to follow the sea, and immediately began to study the wholly unrelated sciences of astronomy and navigation, resolved to become an officer in the French merchant marine. He even succeeded in obtaining appointment to a ship, but relinquished it at the anguished entreaties of his mother and sisters.

At home with his parents in Paris, he found his father's attitude a little dictatorial toward a young man who was already twenty-five years old, and finally made up his mind to leave. The last months of 1830 were spent in the military hospitals of the capital, where before settling down as a teacher he took courses in medicine and the physiology of all that pertained to the voice, since he had been quick to perceive their significance for its rational development. During this period his sister Pauline said that he was in the habit of bringing home the windpipes from all sorts of animals, into which she was instructed to blow vigorously with bellows; what extraordinary sounds were heard then, she continued: clucks, bleatings, and roars that were almost lifelike!

When the young man began his life as a singing master, in 1831, this training stood him in good stead. His insistence that every pupil have a vocal and medical examination, and his scientific method of approach in general, made such a favorable impression that he was surrounded before long by a constantly growing circle of students, and within a short time was named a professor of singing at the Paris Conservatoire.

But because of the Revolution of 1848, or because of turmoil on a smaller scale at home—according to whose account one reads—he left for London in 1850,[4, 8] where he was appointed to a similar position at the Royal Academy of Music, a post that he retained until 1895. For many years he was the leading instructor there, and most great vocalists of the day were his pupils: among them Jenny Lind; Johanna Wagner, niece of the famous composer; and his own two sisters, together with some of the best-

known teachers. Thus as his father had trained a majority of the singers who delighted the ear throughout the first half of the nineteenth century, so he himself was responsible for those whose voices charmed the musical world of the second half.

There, in London, after the death of his first wife, he married again, and lived happily ever afterward—or nearly so, as a lawyer would say, for at the time of his death he was in his one hundred and second year.

Garcia was small of stature, with an olive complexion, a clear-cut and distinguished profile, a lively temperament, a ready wit, an unfailing hospitality, a remarkable patience in teaching, and a habit of rapid gesticulation that plainly betrayed his southern origin. An outstanding feature of his character was an almost abnormal modesty, so profound that he never referred to his laryngeal mirror as a discovery, but only as a simple idea. Rarely could he be persuaded to talk about himself, and he actually denied various details of his life to a niece for fear that she was preparing to write his biography.[8, 10]

In fact there would appear to have been but one flaw in this diamond, and that a negligible one. For all his enthusiasm and affability he is said to have shown a certain reserve that was often misunderstood, and sometimes awoke in his pupils the uneasy suspicion that he recognized only a professional connection with them.

His favorite occupation was the reading of scientific works in German, Italian, Spanish, English, and French, in the course of which this self-taught man had acquired a rich fund of knowledge in almost every field; from time to time, however, he allowed himself other pastimes like the opera, the theater, or a concert. So inordinately fond was he of chess that he often journeyed to Paris for a game with Turgenieff, the Russian novelist and unsuccessful suitor of Pauline. In addition to his native Spanish he spoke English and French fluently, yet on the whole preferred the last. He ate all the ordinary foods, smoked, and enjoyed a glass of wine or beer, but all in great moderation; his lunch, for example, was always the same simple meal: sponge cake and a pint of milk.

At seventy the maestro looked like a man of fifty. Although his voice may have begun to tremble somewhat, he walked quickly, with a light, buoyant step, and his keen, observant eyes would kindle with all the fire and animation of youth as he spoke. He had been gifted with absolute pitch, his ear had remained exceptionally accurate, and he was still a pianist of very fair ability. His activity was amazing; he taught from morning until night, and seemed never to have heard such a word as fatigue.

One day when this extraordinary man was ninety years old some callers found him working in the garden; a little bent with age, frail looking, perhaps, but wiry, with eyes that were still bright and piercing. His moustache was closely trimmed, his white hair partially covered by a red skullcap, and though his speech was rapid every word was clearly pronounced.

For many years an honored guest at the annual dinners of the Laryngological Society of London, he often delighted his hosts with a bright, racy speech, and seldom left before ten o'clock for Mon Abri, his home in a far northwest suburb; a modest dwelling set back somewhat from the street amidst the shade of its trees. It was difficult to realize that he was then almost a centenarian.

That Garcia should still have been giving instruction at the age of ninety-six is remarkable enough; but even more remarkable is it that during all these years he had to break a teaching appointment on only three or four occasions. At the end of a lesson, which sometimes lasted nearly two hours, he would accompany the pupil to the front door with all his old-world courtesy, and there stand chatting for several minutes in defiance of drafts, cold, and damp.

During his one hundred and first year the old gentleman was actually more vivacious than in his nineties; indeed, as Mackinlay says, he seemed to grow younger as he grew older, though naturally enough he was easily tired by exercise. His eyesight was but little impaired, so that he was able to spend a great deal of his time in reading, intensely curious even then about all that was going on in the world. He called on many of his old friends, too, and one day walked up to the fourth floor of an apartment build-

ing, disdaining to make use of the elevator. During the winter of 1905–6, though now nearly a hundred and one, he attended a number of public dinners, and on his birthday celebrated the entrance into his one hundred and second year by seizing a guitar and singing a Spanish song to its accompaniment. A few days later he keenly enjoyed a concert at Queen's Hall.

Garcia ascribed his vigorous old age to mental and physical activity, good digestion, and moderate living, and in respect to the last of these there is no doubt that he was partly right. Osler's terse remark that more men are killed by the knife and fork than by the sword has been abundantly confirmed by experiment on the small animals of the laboratory; those kept on a diet just adequate to maintain health outlive those that are given free access to food. But abstention is not all, by any means; ancestry is a much more important factor in longevity, and Garcia must have had long-lived forbears.

Von Schrötter said that the centenarian's portraits clearly show a tortuosity of the temporal arteries, so that he must have had at least a moderate degree of arteriosclerosis. It would be a miracle if he had not, for few elderly people escape it. Still, although this is a general disease the thickening and hardening may be more advanced in some arteries than in others, and even though the temporal vessels were prominent it is clear enough that the arteries supplying his heart and brain must have been in enviable condition. Else he never could have reached such an advanced age.

Garcia's one hundredth birthday was marked by imposing festivities that began at midday on March 17, 1905, and packed the meeting room of the Royal Medical and Chirurgical Society, in Hanover Square, with delegates of laryngological, musical, and scientific societies, and even of universities.[4] When King Edward heard of the forthcoming celebration he inquired solicitously whether the old gentleman could stand the strain attending personal investiture of the honor that his Majesty wished to bestow: Commander of the Royal Victorian Order. Back came the reply that Señor Garcia was quite ready, and anxious to show his

gratitude for the royal compliment by going himself to Buckingham Palace![10]

Many years before he had been made *Doctor medicinae honoris causa* by Königsberg University, and now the Spanish Chargé d'Affaires invested him with the Royal Order of Alfonso XII, in the name of the King of Spain, and the Emperor of Germany conferred on him the Great Gold Medal for Science. There were illuminated addresses from the Royal Academy of Music, the Royal College of Music, and four other learned bodies; there were addresses and messages from nearly every laryngological society in the world, including those of America and far-off Japan; there were receptions and there were dinners, and honorary membership was conferred by most foreign societies. The celebration was brought to an end with the presentation of a portrait by Sargent, subscriptions for which had come pouring in from physicians and singers all over the world.[4]

How pleasant it would be to think that in addition to all the honors thus showered upon him, a cigar had been named after this great man! But the sad truth is that the Manuel Garcia whose picture has adorned so many cigar boxes was a Cuban manufacturer, not our little maestro.

At the dinners—for the celebration lasted two whole days—the guest of honor ate and drank, wrote Smith, as though he had been more successful in discovering the fountain of youth than his illustrious fellow countryman who sought it in Florida.

Responding to the toast that was drunk to him, Garcia asked the company to imagine how he felt, if they could, and to realize how impossible it was for him to find words that would express his emotions. "Think yourselves each one hundred years old today. Not the ladies. I will not ask them. Though they may come to that they will never look it, and they will never know it, and no one will ever believe it." [4]

The "beloved maestro," the "grand old man who," as Fränkel said so felicitously at the celebration, had "just entered upon the second century of his immortality," [3] died calmly and peacefully in his sleep on Sunday, July 1, 1906.

THE EUSTACHIAN TUBE

THE Eustachian tube is said to have been discovered in the goat some five hundred years before the opening of the Christian Era by Alcmaeon,[1] a follower of Pythagoras, who offered the theory that goats breathe through their ears.[3] This striking idea was not original with Alcmaeon, however, for the medical men of Egypt one thousand years earlier believed that the ears are organs of respiration as well as of hearing, and that the breath of life enters by the right and that of death by the left ear.

In the human subject the Eustachian tube remained unknown until toward the middle of the sixteenth century, when it was described by the famous Bartolomeo Eustachio, an anatomist of Rome. Its name was given in the following century by his countryman, Antonio Maria Valsalva, an anatomist of equal renown.[1]

The tube in question runs from the middle ear downward, forward, and inward to open into the back of the throat above and behind the soft palate, where it flares out like the mouth of a trumpet. Formed partly of bone and partly of cartilage and fibrous tissue, it is from an inch and a half to two inches in length, something like one eighth of an inch in diameter at its narrowest part, and lined by a continuation of the mucous membrane that clothes the nose and throat; hence any inflammation in these cavities is apt to creep up the Eustachian tube and attack the middle ear, announcing its arrival there by the familiar earache.

The canal is usually closed but opens for an instant in the act of swallowing or sneezing, or in certain movements of the jaws such as yawning. Its function is to provide drainage for the middle ear and to keep the air pressure in this cavity balanced against that of the surrounding atmosphere. Under such circumstances the position of the eardrum is normal, but when the tube is

blocked, as by a cold, for example, or by adenoids, the air in the middle ear is soon absorbed, a partial vacuum is created, and as a consequence the drum membrane is pushed inward by the pressure of the air outside. In accordance with the degree of obstruction the result is a feeling of stuffiness in the ears; more or less impairment of hearing; a little dizziness, especially if only one tube be closed; and ringing, crackling, or popping noises; the voice may reverberate in the head and the patient be conscious of a sound when he breathes. In most cases his symptoms clear up within a short time, but should the stoppage persist or become chronic expert care is required, since the outcome may be disastrous.

Obviously the treatment is to open the affected tube, or tubes, a procedure for which several means are available. Valsalva's method, which is rediscovered sooner or later by every child, consists in attempting to exhale forcibly while pinching the nostrils together and keeping the lips tightly closed. An amusing crackle follows. The process is simple, to be sure, but dangerous when the nose or throat is inflamed, since infectious material may be forced up the tube and into the middle ear. By a method somewhat similar to Valsalva's air is blown in by the physician from a rubber bag, the nozzle of which is inserted into a nostril. The best treatment of all, however, is catheterization, because it can be limited to the tube involved and the pressure can be accurately regulated. Under local anesthesia a small silver tube, or catheter, so thin that it can be bent to conform to the individual patient, is passed along the floor of the nose to the back of the throat, withdrawn slightly, and then gently manipulated until its tip is felt by the operator to enter the orifice of the Eustachian tube. Air, or an appropriately medicated fluid, is then injected.

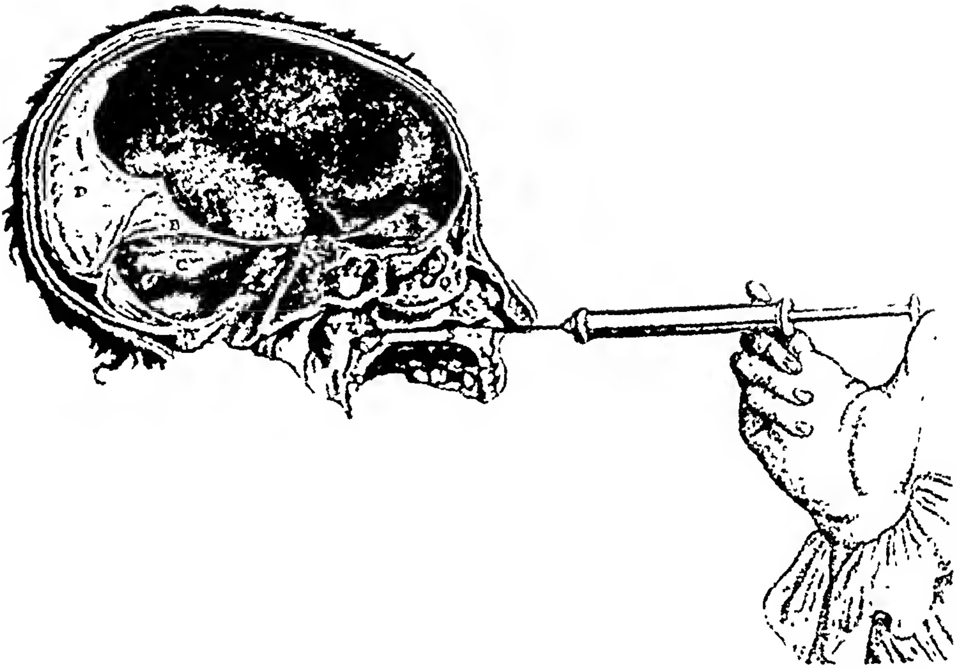
For some time prior to the year 1724 Monsieur Edmé Gilles Guyot, postmaster at Versailles, had been troubled with deafness, for the relief of which he had sought the advice of physicians in vain.[7] Thrown on his own resources he made the first real contribution to the treatment of diseases of the ear, though the discovery should have come about years earlier because of

the rich fund of anatomical knowledge that existed even before his day.[8] Thus in 1683 J. G. du Verney, one of the greatest of the seventeenth-century anatomists, had published a treatise on the ear that has been called little short of phenomenal for its time. Lacking all modern methods of investigation, he correctly described, among other things, the Eustachian tube and its function and expressed his disagreement with the still current idea that it served for both hearing and breathing.

Guyot may have been familiar with this book, for he is said to have possessed a wide knowledge of anatomy that had been acquired through simple curiosity. But in any case his own need led him to study minutely the structure of the ear, and having conceived the hope of curing himself by opening the Eustachian tube he had an apparatus constructed after his views, and through its use is said to have recovered his hearing.

It would have made the modern specialist shudder, consisting as it did of a double pump with a common reservoir and operated by two cranks turning in opposite directions. A leather connection led from this contrivance to a tin tube with a sharp bend, designed to be introduced through the mouth above and behind the soft palate and thence into the Eustachian tube.[5]

Guyot demonstrated his apparatus before the Académie des Sciences de Paris in 1724. The members listened with polite attention, but it is clear that they entertained serious doubts as to its value, for they agreed that Monsieur Guyot's instrument was highly ingenious and would no doubt serve to wash out at least the mouth of the Eustachian tube, which would make it very useful in some cases. Sabatier, a prominent physician of his day, joined in this damning with faint praise. He thought that it would be difficult, if not impossible, to enter the Eustachian tube through the mouth, and that the patient would be annoyed and the operator seriously inconvenienced by the gagging and vomiting induced by the presence of a metal tube in the throat. Nevertheless, he continued, the method was worthy of recognition, and the praise bestowed on it by the Académie and by the most distinguished members of the medical profession was as just as it was well merited.[5]



WATHEN'S ILLUSTRATION OF HIS METHOD OF CATHETERIZING THE EUSTACHIAN TUBE

Once the question had been broached a few physicians continued the endeavor to reach the Eustachian tube by way of the mouth. The procedure was abandoned before long, however, in favor of the much easier nasal route, introduced seventeen years later, in 1741, by Archibald Cleland, an English army surgeon. He made no mention of Guyot, and his own paper in its turn escaped almost entirely the attention of his contemporaries, which is not surprising in view of the inadequate means of communication available in his day. Just as he himself was unaware of Guyot's work, so Antoine Petit, in 1753, and Jonathan Wathen, in 1756, wrote of discovering catheterization of the Eustachian tube through the nose without mentioning Cleland.[7] The new procedure, including the use of a flexible silver tube, was not wholly unlike that employed at the present time except, of course, that modern methods of local anesthesia were still unknown.

VIII

EYEGLASSES AND SPECTACLES

An object is seen because it emits particles of itself that bombard the eye.[23] At least that is what Democritus and his school thought, and they were wrong.

Other Greek philosophers believed that the the eye sends out feelers, as it were, which run out to the object and come hurrying back with the desired information. And *they* were wrong.

A third group, with admirable caution, adopted a more or less middle course and taught that feelers are projected, indeed, but that before they reach the object of investigation they meet particles of light from it and, having received their intelligence in mid-air, return with it to the eye. This was better, for they may have been partly right.

Speculation rather than experiment ruled until the eleventh century, when Alhazen, an Arabian mathematician and the first great discoverer in optics after Ptolemy, made the earliest scientific examination of the camera obscura, which in his day had no lens. He was well acquainted with the projection of images of objects through a small aperture, and was the pioneer in showing that the camera obscura is, in effect, a model of his eye; that the casting of an image on the retina corresponds with the passage of light from an object through the minute opening of the instrument and its arrival on a screen. Several hundred years later Francesco Maurolycus, a celebrated mathematician of Messina, declared that the retina is the essential organ of vision, and not the crystalline lens, as Galen the physician had believed.

Leonardo da Vinci, painter, sculptor, architect, musician, engineer, and natural philosopher, followed the same path in a manuscript that was discovered only in 1797. In explaining how the camera obscura illustrates the phenomena of vision he discarded the view still held by his contemporaries, according to

which the eye throws out rays that touch the object it wishes to examine.

It is impossible that the eye should project from itself, by visual rays, the visual virtue, since as soon as it opens, that front portion of the eye which would give rise to this emanation would have to go forth to the object, and this it could not do without time. And this being so, it could not travel so high as the Sun in a month's time when the eye wanted to see it . . . . . . and if this virtue would have to travel through the air as perfumes do, the winds would bend it and carry it into another place.

Why didn't some Greek think of that?

The light by which we see has been for centuries a vexation and perplexity to mathematicians and physicists alike, who now are embarrassed by two explanations; embarrassed because two are far from being twice as good as one.

The first interpretation, advanced by Newton in 1675, held that light corpuscles are continuously discharged from every luminous point in the universe, to impinge on the retina either directly or after having been reflected.

To remedy the many defects in this emission hypothesis Huygens, a Dutch physicist, proposed the wave, or undulatory, hypothesis, created only a few years after Newton's but not published until 1690. Already propounded in a vague way by Robert Hooke, that highly talented but eccentric experimental physicist, this theory conceived of light as a series of waves sent out into a hypothetical luminiferous ether. For its time, at any rate, it explained fairly well the chief phenomena of light, but before long it gave rise to a bitter war of words that lasted for more than 160 years and beside which the ancient grudge between the Montagues and the Capulets or the feud between Guelphs and Ghibellines was a veritable love feast. At last, however, the wave theory gained the ascendancy, as a result of support from three different directions: Roemer's announcement, in 1675, that light has a finite velocity, which he set at 186,000 miles a second; the discovery of the interference of light, in 1801, by Young; and of the polarization of light by Fresnel, in

1816. But Roemer's conclusions had been rejected by nearly all the prominent scientists of his day, and more than fifty years had passed before they were confirmed and accepted.

Maxwell's theory, advanced in 1864 and since proclaimed the most important contribution of the nineteenth century to physics, suggested on purely theoretical grounds that the waves of light are electromagnetic. It received but little support, however, until it was experimentally verified a quarter of a century later by Hertz, who produced short radio waves and proved that they can be reflected, refracted, and polarized as can light. Then came Roentgen's discovery, in 1895, of the waves bearing his name, followed by that of radioactivity and finally of the cosmic rays, shortest and most penetrating of any so far revealed.

All the forms of known energy except gravitation and mechanical energy have turned out to be identified with electricity, since they are waves of electromagnetism differing from one another only in length. But in 1900 Lebedev showed that light exerts pressure on a surface upon which it falls, as was to have been expected from Newton's corpuscular theory.[13] If so, has it not mass, and is it not therefore matter? The answer appears to be yes, for the demonstration of the quantum and Einstein's quantum theory of light, as well as modern views on atomic structure and radiant absorption, all point to the conclusion that matter and energy are one, and that they are electrical in nature.

At present both the corpuscular and the wave theory seem to be true, and the difficulty is best resolved, perhaps, by following the example of the prominent physicist who said in effect that he believed in the one on Mondays, Wednesdays, and Fridays, and in the other on Tuesdays, Thursdays, and Saturdays.

Even the omniscient Samuel Johnson could not tell what light is. When Boswell asked him to define poetry he replied: "Why, Sir, it is much easier to say what it is not. We all *know* what light is; but it is not easy to *tell* what it is."

The riddle of light itself belongs to physics, of course, but even the work on vision and its correction has been carried out largely by physicists, aided by mathematicians, astronomers, and monks, with an archbishop thrown in here and there for good measure.

Little of the fundamental investigation has been done by physicians.

Whatever it may ultimately prove to be, light passes through the cornea and enters the pupil to reach the lens, which lies just behind it and is the equivalent of a convex glass lens, as was demonstrated in the sixteenth century by Vesalius, anatomist and physician.[22] In the normal eye both cornea and lens have a regular spherical curvature; hence they do not distort the rays but bring them to a precise focus on the retina, where their energy is mysteriously transformed into visual sensations. The remark has been made [13] that it would be strange indeed if normal eyes were common, for normality depends upon precision to a hair's breadth in the length of the organ and the shape of cornea and lens, and such mathematical exactitude is rarely achieved in living organisms. Thus the emmetropic, or normal, eye is far less commonly encountered than the ametropic, or abnormally shaped, which cannot focus light rays exactly on the retina.

The usual departures from normal are three in number. In farsightedness, or hypermetropia, the rays come to a focus behind the retina because the eyeball is relatively too short. In the opposite condition, nearsightedness, shortsightedness, or myopia, the eye is too long relatively, and the point of sharp focus is therefore in front of the retina. Myopia, from two Greek words meaning to shut the eyes, recalls vividly the squinting eyes of the nearsighted, half closed to aid vision in the absence of suitable correcting lenses. In the third anomaly, astigmatism, there is no single point of clear focus because the surface of the cornea, or occasionally of the lens, is not truly spherical.

The farsightedness of age, presbyopia, or old man eyes, is not caused by a malformation of the eyeball, but usually by a loss of elasticity in the lens that prevents it from being focused on near objects; much less often it results from weakness of the ciliary muscle. This variety was first clearly distinguished from hypermetropia in 1859 by Donders, the great Dutch ophthalmologist.

All these conditions can be wholly or partly relieved in most patients: hypermetropia and presbyopia with convex spherical

lenses, myopia with concave spherical lenses, and astigmatism with cylindrical lenses.

Now a spherical flask filled with clear water is a lens, obviously a convex spherical one, and the old Greeks and Romans were thoroughly familiar with the magnifying properties of such a vessel; it has been suggested, too, that the fine work being done in Egypt on gems and gold even two thousand years before Christ would have been impossible without help of this sort. These flasks were used also as burning glasses by physicians of the olden time, and the greatest surprise was expressed that they could act in this capacity though filled with cold water; for their effect was attributed to their contents and not to the curved surface of the glass.[8]

The convex spherical lens has had a long and honorable career. In the thirteenth century Roger Bacon was aware that objects are magnified when only segments of spheres are placed on them, and he is thought to have been the first to recommend such a lens as an aid to vision. A Roman over fifty years old could overcome the miseries of his presbyopia only by getting someone to read to him, but the dawn began to break when Bacon wrote: "For this reason such an instrument is useful to old persons and to those with weak eyes, for they can see any letter, however small, if magnified enough."[16]

The concave spherical lens, unknown to the ancients, was also familiar to Bacon and to his contemporary and fellow Franciscan, John Peckham, later Archbishop of Canterbury.[8] Comparative silence followed, however, until toward the end of the sixteenth century, when Johannes, another Archbishop of Canterbury, mentioned it clearly and Giovanni della Porta, a leading scientist of his day and one of the founders of modern optics, explained its use in myopia. Not so many years before this Maurolycus had discussed the laws of optics and the nature of far and near vision, and about a hundred years later the theologian and astronomer, Johannes Kepler, who was himself nearsighted and who did so much to advance the knowledge of physiological optics, suggested that in shortsightedness the retina is farther away from the lens than it should be.[11] But it was well beyond the middle of

the nineteenth century before ophthalmologists were able to advance definite proof that myopia actually is caused by an elongation of the visual axis.

Astigmatism was correctly attributed in 1801 to irregular refraction, by Thomas Young, English physician and man of science, who had found this abnormality in his own eyes eight years previously.[11, 24] But he was more interested in other things, failed to realize the importance of his discovery, and did nothing more about it. The name was given later by William Whewell, mathematician, historian of science, and Master of Trinity College, Cambridge.[12] The unevenness responsible for astigmatism may be in the crystalline lens—it was in Young's case—but more often affects the surface of the cornea, as has already been said. If it be the result of an ulcer the surface is so distorted that no lens will help, but this acquired, irregular type is fortunately rare in comparison with the ordinary congenital, or regular, type. Here the asymmetry is uniform, and the cornea generally flatter from side to side than it is from above downward. Different areas therefore bring the light rays to a focus differently, the more curved meridian acting as a stronger lens, and the image of a luminous point appears on the retina as a line, an oval, or a circle, but never as a point.[18, 21] Hence the name, astigmatism, or "no spot."

This refractive error, though discovered by a physician, was first corrected by an astronomer who, afflicted with the corneal type, showed that it can be relieved with a cylindrical lens. Such a lens may be thought of as sliced from a cylinder on its long diameter; when the outer surface is employed the lens clearly will be convex, whereas the inner surface of a hollow cylinder will give a concave cylindrical lens.

Sir George Biddle Airy, Astronomer Royal from 1835 to 1881, was of medium stature and sound constitution, self-reliant, fearless in debate, and unusually systematic in his personal affairs.[1, 17] He never threw away an old checkbook, a letter, or even a circular, and ascribed to this high appreciation of method his command of mathematics, which, he used to say, was no more

than order carried to a considerable extent. He was eminently practical and impatient of theory, characteristics that kept him incessantly at war with some of the Cambridge mathematicians.

He was born at Alnwick on July 27, 1801, and thus by a curious coincidence in the very year when Young first described astigmatism. As his parents were always in restricted circumstances he was dependent from the first largely on his own efforts, and defrayed all his expenses in college by tutoring. When he entered Trinity College, Cambridge, in 1819, it was as a sizar, a poor student who was exempted from certain charges like dinner in hall and, as Macfarlane pathetically explains in a biographical sketch, dined after all the rest on the remains of the Fellows' dinner. Having made a brilliant record, he was graduated in 1823 and became successively a Fellow of his College, Professor of Mathematics, Professor of Astronomy, and finally Astronomer Royal.

From the very first he was especially interested in mathematics, optics, and astronomy, and had brought with him to Trinity a telescope of his own making. "Long before I went to College," he wrote in his *Autobiography*,

> I understood the action of the lenses of a telescope better than most opticians. . . .
>
> On April 8th [1822] I intended to write an account of my eye: I was then tormented with a double image, I suppose from some disease of the stomach: and on May 28th I find by the drawing of the appearance of a lamp that the disease of my eye continued.
>
> On August 25th [1824] I made an experiment on my left eye, with good measures, and on Aug. 26th ordered a cylindrical lens of Peters, a silversmith in the town, which I believe was never made. Subsequently . . . I ordered cylindrical lenses of an artist named Fuller, living at Ipswich, and these were completed in November, 1824. . . .
>
> On Feb. 5th [1825] I finished a Paper about the defect in my eye, which was communicated to the Cambridge Philosophical Society on Feb. 21st.

This paper [2] bore the title: "On a peculiar Defect in the Eye, and a mode of correcting it," and he appears not to have known

of Young's description, for it opens with the remark that the malformation in question was probably not uncommon, though until then unnoticed.

Two or three years since I discovered that in reading I did not usually employ my left eye, and that in looking carefully at any near object, it was totally useless: in fact, the image formed in that eye was not perceived except my attention was particularly directed to it. Supposing this to be entirely owing to habit, and that it might be corrected by using the left eye as much as possible, I endeavored to read with the right eye closed or shaded, but found that I could not distinguish a letter, at least in small print, at whatever distance from my eye the characters were placed. No further remark suggested itself at that time, but a considerable time afterwards I observed, that the image formed by a bright point (as a distant lamp or star) in my left eye, was not circular, as it is in the eye which has no other defect than that of being near-sighted, but elliptical, the major axis making an angle of about 35° with the vertical. . . . Upon putting on concave spectacles, by the assistance of which I saw distant objects distinctly with my right eye, I found that to my left eye a distant lucid point had the appearance of a well defined line. . . . I found also that if I drew upon paper two black lines crossing each other at right angles, and placed the paper in a proper position, at a certain distance from my eye, one line was seen perfectly distinct, while the other was barely visible. . . .

Here Airy anticipated the astigmatic dial, or fan, so familiar to anyone who has ever been examined for glasses, in which the radiating lines should all be seen with equal clearness, but are not by the astigmatic eye. When the astigmatism is regular the most distinct and the least distinct line are at right angles one to the other, exactly as he said.

All these appearances indicated, he continued, that the refraction of the eye was greater in the plane nearly vertical, than in that at right angles to it, and that consequently it would not be possible to see distinctly by the assistance of lenses with spherical surfaces. . . .

My object now was to form a lens which should refract more powerfully the rays in one certain plane, than those in the plane at right angles to it; and the first idea was to employ one whose surfaces should be cylindrical and concave . . . but for the facility of

grinding . . . it appeared preferable to make one surface cylindrical, and the other spherical; both concave.

Having adduced some brain-splitting optical formulas, Airy went on as follows:

To discover the necessary data, I made a very fine hole with the point of a needle in a blackened card, which I caused to slide on a graduated scale; then strongly illuminating a sheet of paper, and holding the card between it and the eye, I had a lucid point upon which I could make observations with great ease and exactness. Then resting the end of the scale upon the cheek-bone, and sliding the card on the scale, I found that the point . . . appeared a very well defined line. . . .

After some ineffectual applications to different workmen, I at last procured a lens . . . from an artist named Fuller, of Ipswich. It satisfies my wishes in every respect. I can now read the smallest print at a considerable distance with the left eye, as well as with the right. I have found . . . that the eye which I once feared would become quite useless, can now be used in almost every respect as well as the other.

. . . After many inquiries I have not been able to discover that this construction has been used to correct any defect in the eye, or even that a defect similar to that which I have described, has ever been noticed. In laying before this Society the notices of a case which appears at once novel and important, I trust that I shall not be thought to have trespassed unprofitably upon their time.

As he lived for sixty-seven years after this, dying in 1892 at the age of ninety, he must have had the intense satisfaction of knowing that the time of the society had not been wasted on that February evening.

He reported in 1846,[3] and again in 1867,[4] that although there had been a change in his myopia there had been little in his astigmatism.

By 1860 or thereabouts cylindrical lenses had come into general use. At first they were mounted in round frames, so that they could be rotated by the wearer until the position had been found that seemed most effectively to correct the asymmetry, but such a crude measure as this is no longer employed.[12] The lenses

are now firmly secured in a position that is properly determined by the prescriber, and not by the patient himself.

The invention of eyeglasses has been variously attributed to the Chinese, to the Romans, and to Roger Bacon. Garrison thought, however, that the Chinese learned of them from India, whereas Chance wrote that according to a Chinese encyclopedia they were introduced by Spanish Jesuits.

No doubt the Romans have received the credit because Nero is said to have watched the gladiatorial contests with an emerald, this vague reference having been interpreted to mean that he used glasses.[8] But nothing known of him, from writings or from effigies in stone or on coins, suggests that he was either nearsighted or farsighted, though his eyes were certainly "weak," perhaps from astigmatism or albinism. The emerald with which he viewed the struggles of the gladiators may have been used to look through, or into as a mirror, but in which of these two ways it was employed has not come down to us. Nothing is actually known of its size, nor is there any evidence to show that it had been ground into the form of a lens. It might have served as an amulet, in accordance with a belief then current, to strengthen his eyes; or, if his trouble were albinism, to protect them from the glare of the arena, since the grateful effect of green had been recognized from time immemorial. Again, it is possible to connect the use of a green gem with the political inclinations of the Emperor, which are known to have favored the Green party and to have been expressed by the color of his raiment and the sprinkling of the arena with green sand. But whatever the reason, his emerald could not have been employed to aid distant vision as are the modern convex lenses of long focus, because the Romans of those days, like the Jews and the Greeks, were not acquainted with such lenses. The only ones brought to light by excavations at Nineveh, Pompeii, and other sites have been of such short focal length that they would have been entirely useless except as magnifying or burning glasses—the purpose for which they were made.

As for Bacon, he may have gone further than merely to recom-

mend a convex lens for easier reading, or he may not; the question has never been really settled.

The truth is that nobody knows who did invent eyeglasses. Search for evidence of their employment on the continent of Europe in the early Middle Ages has been fruitless, and although they were mentioned occasionally in old wills from 1372 onward, no specimen prior to 1500 has been preserved in England.[16] At any rate, they were in use toward the middle of the fourteenth century, and greatly facilitated the revival of learning, for the period of their introduction coincided with the rediscovery of the Greek and Latin classics and the invention of printing. They did away, too, with the thick lettering of the medieval manuscripts and the heavy type of the early incunabula, which were designed for elderly presbyopic readers.

The most direct information on their invention seems to come from Italy, where two names are especially mentioned: Salvino d'Armato degli Armati, scion of a prominent family; and Alessandro della Spina, a Dominican monk.[8] The date of d'Armato's invention is given as 1285 and the inscription over his grave reads, in translation: "Here lies Salvino d'Armato degli Armati, of Florence, the inventor of eyeglasses. God forgive his sins. Died A.D. 1317." Even this evidence seems unconvincing to Albertotti, the Italian historian of ophthalmology, and as Samuel Johnson maintained that in the matter of lapidary inscriptions a man is not on oath Albertotti may be right. But if d'Armato really did invent eyeglasses, and if he had any sins, they must have been forgiven long since, for these aids to vision are among the greatest of all gifts to mankind.

An old manuscript in the Monastery of Saint Katherine, in Pisa, gives the date of della Spina's death as 1313, and says that he made eyeglasses; and there is still other evidence to show that they first appeared toward the end of the thirteenth century. In his history of spectacles Emil Bock wrote that Giordano da Rivalto, a celebrated preacher of the times and a confrere of della Spina, said in a sermon on February 23, 1305: "It is not twenty years since one of the most useful arts in the world, the art of making eyeglasses to give better vision, was discovered.

. . . I myself have seen and talked with him who invented them and first made them." But whether he was referring to d'Armato, or to della Spina, or even to some third person, is not clear.

While much of the evidence goes to suggest, therefore, that eyeglasses actually were invented in Italy toward the end of the thirteenth century, and by d'Armato and della Spina, either independently of one another or in concert, it is known nevertheless that old people in Germany were using them at this time, and that they were enjoyed also in Flanders. Considering the difficulties of travel and communication at that period it may well be asked whether glasses really were invented in Italy alone, or whether other countries, too, may not share the credit. Most of the champions of the two Italians have pushed the claims of others into the background, notably that of Roger Bacon, to whom some give the preference. There is much to be said for the English friar. Thus it has been related, for example, how Heinrich Goethals, teacher of theology and philosophy and a close friend of Bacon, was sent to Rome to discuss with Pope Martin IV some affairs of his Order. On his journey through Italy he was overtaken by the news that the head of the Church had died, and so that his long trip might not have been taken in vain he stopped over in Florence or in Pisa, which are only about forty-five miles apart, to await the choice of a new Pope. Here he became acquainted with della Spina, to whom he may have imparted the news that the *Doctor mirabilis* had found a convenient aid to vision. But Bacon's discoveries were cried down as works of the Devil, and he had a particularly bad name in Italy because he condemned often and openly the corruption of the clergy; hence a monk might well have preferred not to mention an inventor who was in such bad repute.

Concave lenses came into general favor much later than the convex. Though Pope Leo X was portrayed with concave glasses by Raphael in 1475, and these were in limited use by the middle of the sixteenth century, they were not widely employed until the eighteenth. If there were objection to convex lenses on the score of vanity, as there was, what must the feeling have been toward the heavier concave ones?

In what are called with mistaken regret the good old days, eyeglasses were sold by street hawkers from booths or barrows, when they were not peddled about on trays, and the buyer selected the pair that he devoutly hoped would give him the greatest measure of relief; until the nineteenth century the age for which they were supposed to be suitable was scratched on the lenses, a specification that was wholly arbitrary and founded upon inadequate experience in even the most favorable cases. As the laws of optics remained shrouded in mystery until long after the invention of eyeglasses, these were credited in the West no less than in the East with such mysterious powers as restoring sight to the blind, or enabling him who wore them to see into the future. Dishonest dealers were not slow to make the most of all this, charging an unreasonably high price for glasses that they said would not only give distinct far and near vision but even enable those to read who had never learned the art; and the nineteenth century had almost run its course before any more honest or skilled advice was attainable than that of the peddler, or later the more reliable optician, who sold them.

Eyeglasses were first mentioned from a medical standpoint in 1305 by Bernard of Gordon, celebrated teacher at the medical school of Montpellier, but he said that they were rendered unnecessary by his ophthalmic remedy, a preparation so remarkable that it made those with poor vision able to read even small letters without them. Probably he was more ignorant than avaricious, however, since nothing was known in those days of refraction within the eye; hence, no doubt, this unwarranted optimism. A younger contemporary, Guy de Chauliac, most famous surgeon of the Middle Ages, was more cautious, for though he extolled the lotion he explained that the patient must ultimately come to glasses should it prove to be of no avail. The first physician to show any real confidence in the new aids to vision was Montanus, but the example of this great Italian clinical teacher of the Renaissance went unheeded, and they made their way slowly. Not only did his colleagues fail to recommend eyeglasses; they actually advised against their use, as did Bartisch,

of Dresden, who published in 1583 the first German book on ophthalmology. For years physicians paid not the slightest attention to them, and even into the nineteenth century oculists thought of themselves as medical men, considered the fitting of glasses beneath their dignity, and preferred sending their patients to an optician. With a changed professional attitude, however, and an increased number of specialists, this practice has been virtually discarded by oculists; in fact their painstaking correction of refractive errors has been called one of America's greatest gifts to the ophthalmologists of the Old World.

The endeavor to devise a frame in which lenses could be conveniently worn was a truly amazing struggle in retrospect. First came the reading glass for old people, a single round lens in a metal frame that was provided with a long handle; then, late in the fifteenth century, someone conceived the idea of using two lenses. Each had its own separate handle, and the pair were fastened at their lower ends to form a V, sometimes by a rigid joint, sometimes by a movable one that permitted the handles to be closed together. But this frame was still held in the hand.

In an earlier variety, two round frames were joined by a clumsy curved connecting piece, though this ancestor of the pince-nez was not yet designed to ride upon the nose. Savonarola recommended fastening it to the peak of a cap that could be pulled well down over the forehead, which gave rise to the witticism that it would be suitable only for princes, who did not have to doff their caps. No one had realized yet that noses were made to hold our glasses, as Voltaire said long afterward.

At the beginning of the fifteenth century, too, appeared the first spectacles, as distinguished from the pince-nez or eyeglasses. Heavy frames of wood or leather were held in place by strings or prolongations of the leather itself passing back behind the ears; awkward contrivances that were eventually replaced by frames of gold, silver, steel, whalebone, or horn of various colors. Sometimes they were provided with bows to go over the ears, but the whole so clumsily made as to resemble the work of a blacksmith

rather than of an artisan, and these lasted until the end of the century. More delicate bows then made their debut, though nothing to equal the spectacles of today is found until the 1830's.

As late as the beginning of the nineteenth century the Chinese employed curious variants, in which round frames with their connecting nosepiece were retained in position by weighted cords

Old Chinese Spectacles with Weighted Cords

that went behind the ears and then came forward to hang over the chest; or by loops around the ears and a wire support extending from the nosepiece to the forehead, against which its mushroomed end rested.

Certainly it was no part of the physician's duty to design frames for eyeglasses and spectacles; but one thing that he might have done, the invention of bifocal glasses, was left to that universal genius, the American Leonardo da Vinci, Benjamin Franklin. Like everyone else of his day who needed separate lenses for far and near vision, he carried two pairs of spectacles; like everyone else, too, he found it inconvenient to change from one to the other; but unlike everyone else he had the ingenuity

Old Chinese Spectacles with Wire Support

required to solve this problem, and the way in which he did so is described in two letters to his friend George Whatley, the philanthropist, of London.[14] The first one, written from Passy on August 21, 1784, concludes as follows:

Your eyes must continue very good, since you are able to write so small a hand without spectacles. I cannot distinguish a letter even of large print, but am happy in the invention of double spectacles, which, serving for distant objects as well as near ones, make my eyes as useful to me as ever they were. If all the other defects and infirmities of old age could be as easily and cheaply remedied, it would be worth while, my friend, to live a good deal longer. But I look upon death to be as necessary to our constitutions as sleep. We shall rise refreshed in the morning.—Adieu, and believe me ever,

Your's most affectionately,
B. Franklin.

His friend had said that he was "rising 75," and on May 23, 1785, Franklin replied: ". . . but I am rising (perhaps more properly falling) 80 . . ." This letter takes up sundry matters of interest to the two old friends, including a description of his in-

vention and a discussion of its criticism by Dollond, a famous optician of London.

By Mr. Dollond's saying, that my double spectacles could only serve particular eyes, I doubt he has not been rightly informed of their construction, I imagine it will be found pretty generally true, that the same convexity of glass through which a man sees clearest and best at the distance proper for reading, is not the best for greater distances. I therefore formerly had two pairs of spectacles, which I shifted occasionally, as in travelling I sometimes read and often want to regard the prospects. Finding this change troublesome, and not always sufficiently ready, I had the glasses cut out and half of each kind associated in the same circle, the least convex, for distant objects the upper half, and the most convex, for reading, the lower half: by this means, as I wear my spectacles constantly, I have only to move my eyes up or down, as I want to see distinctly far or near, the proper glasses being always ready. This I find more particularly convenient since my being in France; the glasses that serve me best at table to see what I eat, being the best to see the faces of those on the other side of the table who speak to me, and when one's ears are not well accustomed to the sounds of a language, a sight of the movements in the features of him that speaks helps to explain; so that I understand French better by the help of my spectacles.

Franklin's invention was the prototype for today's lens with an invisible added sector. The first improvement was one of the few radical measures to be proposed by a physician, Dr. George C. Harlan, of Philadelphia: the cementing to the lower part of the distance lenses of oval or circular glass wafers carrying the correction for near work.[11] Their edges could be seen, however, and lenses with cemented additions were finally supplanted by others in one piece, made by fusing the two corrections or by grinding them on a single piece of glass.

The latest word in visual aids is the contact lens, a delicate shell applied directly to the cornea. This boon to those who appear on stage or screen is the invention—again—of an astronomer: John Frederick Herschel, who attempted its manufacture as far back as 1827.[11]

IX

THE ITCH

THE itch, or scabies as it is more elegantly known among physicians, from the Latin *scabere*, to scratch, was tormenting the human race in Biblical times if not before. In those days "leprosy" included a number of skin diseases, and there is good reason to believe that scabies was among them. Early Greek writers referred to it, as did the physicians of the Arabian school about the tenth century, though no doubt other irritating disorders of the skin were still confused with it. It was extremely common throughout Europe in the Middle Ages because of the crowded conditions in the walled medieval towns, the general ignorance and unclean habits of the masses, the gross immoralities associated with the many wars, and the hordes of wandering soldiers and students who did their best to facilitate its dissemination.[6] In both World Wars the disease was a serious problem in military medicine.

Dr. Reuben Friedman, the American authority on the history of scabies, from whose writings most of the material for this chapter has been gathered, thinks that the disease probably did not exist in North America before the arrival of the colonists at Plymouth and Jamestown.[2] In any case it was only too common later in the colonies. Benjamin Franklin's *Pennsylvania Gazette* carried advertisements in 1731 of "An Ointment for the ITCH," inserted by his mother-in-law, the Widow Read, then living with her recently married daughter and son-in-law. The ingredients of her cure are unknown today but one was probably sulphur, which even then had been successfully used for many years and is still one of the most effective means of combating the disease. Like her distinguished son-in-law she was ahead of her time, for the physicians of that day regarded the itch as an internal disease,

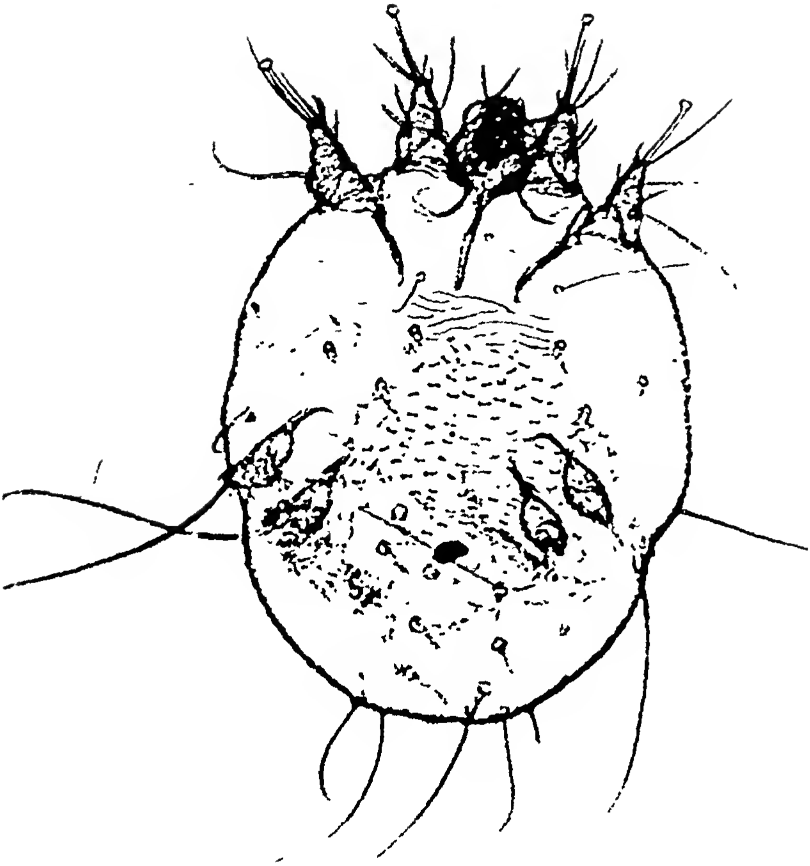
treated it in consequence with bleeding, dieting, and purging, and scorned the use of ointments. Her advertisement runs:

THE WIDOW READ, removed from the upper End of High-street to the *New Printing-Office* near the Market, continues to make *and sell her well-known Ointment for the ITCH, with which she* has cured abundance of People in and about this City for many Years past. It is always effectual for that purpose, and never fails to perform the Cure speedily. It also kills or drives away all Sorts of Lice in once or twice using. It has no offensive Smell, but rather a pleasant one; and may be used without the least Apprehension of Danger, even to a suckling Infant, being perfectly innocent and safe. Price 2 *s.* a Gallypot containing an Ounce; which is sufficient to remove the most inveterate Itch, and render the skin clear and smooth.*

Scabies was rather prevalent in the United States during and after the Civil War, especially among the soldiers. In the following two decades its incidence decreased greatly, only to rise once more during the middle and late 'eighties with the increase of immigration from southeastern Europe, whence came a group with standards of cleanliness far below those that had previously obtained.[3]

Even today, long after the discovery of its cause and cure, scabies continues to be one of the most common skin diseases seen in hospital practice. Among private patients it is less often observed, for it is a disease of filth, carelessness, and overcrowding and the educated and cleanly therefore escape unless through some unusual perversity of fate. Nevertheless, there is a legend that Napoleon Bonaparte was infested.[4] Friedman thinks it unfounded, however, because although the disease is highly contagious there is no evidence that the Empress Josephine or her son or daughter, Eugène and Hortense de Beauharnais, or any other member of the Imperial household ever had it. He believes, therefore, that the Emperor must have been troubled with some other irritating disease of the skin, for in those days dermatology was hardly yet even in its infancy and diagnosis was naturally uncertain to the highest degree. So while Napoleon may well have had an itch, he probably did not have THE itch.

* *Courtesy of the Historical Society of Pennsylvania,* Philadelphia.



FEMALE ITCH MITE. GREATLY ENLARGED

The amusing suggestion has been offered that his characteristic posture with one hand inside the lapel of his coat was symbolic, as it were, of his itch, but this seems more a pleasantry than a serious proposal and the position is far more apt to have been simply a mannerism.

Even into the early nineteenth century it was believed by some prominent physicians that the presence of scabies would cure certain serious diseases such as epilepsy and tuberculosis. But this, the only good thing ever said about the itch, turned out of course to have been wrong.

Though a picture of *Acarus scabiei*, the causative organism, looks like an insect, the itch mite is not one, for it has no antennae; its head, thorax, and abdomen are fused into one; and it has four pairs of legs as against the insect's three.[8]

Scabies follows the deposition of an impregnated female on the skin after contact with a person who has the disease, or occasionally with infested articles such as gloves, bed linen, or towels. But as few itch mites live longer than a week after having been separated from a human host, the former mode of transmission, from person to person, is by far the more common. Indeed, even when conditions were made as favorable as they could be Kenneth Mellanby succeeded only twice out of sixty-three trials in giving scabies to volunteers by means of infested underclothing and blankets. On the other hand, even the slightest personal contact served as an efficient means of spreading the disease.

Once having arrived on its new host the mite begins to burrow into the skin at some site that appeals to it, most often the webs between the fingers, the wrists, the anterior folds of the armpits, and so on; [8] in children it is often the palms and soles. The face and scalp are rarely attacked. The little pest is rather particular in the selection of its new home and if confined under a cell on the forearm, say, will tunnel deeply enough for immediate concealment only; if the cell be removed the invader will leave instantly for a more favored site like the wrist. It can hide itself in the skin in about two minutes and a half, after which its movements depend upon the temperature of the part. If this be cooled

the animal will cease to burrow, but will resume operations at a speed of something like one tenth of an inch daily if warmth be applied. The rate of burrowing is regulated, therefore, by the temperature of the region attacked, and this accounts for the intolerable itching at night, when the patient is warm in bed, as well as for its relative or even complete absence during the day.

Egg laying begins almost simultaneously with burrowing, and it has been estimated that from one to four ova are deposited daily over a period of from four to six weeks, the total number being set at about forty or fifty. All the figures given, however, are based on estimates and so are admittedly uncertain. When her time has come the female dies in her burrow, and a second mating never takes place. Thus, as Friedman says, in preparing her home the acarus also digs her grave.

The shell of the eggs ruptures between the third and the sixth day and the young females and somewhat smaller males emerge through the open end of the burrow or through openings in its roof.[12] As the males are fewer in number, one may fertilize several females. It is after fertilization that the female forces her way into the skin, producing the characteristic burrows, tunnels, or galleries in its outermost layer. The males also may live in these tunnels, but are more often found in the skin outside them.

Unless they are exceptionally light in color the burrows can easily be seen with a hand lens as whitish, yellowish, or darkish threads, slightly curved, tortuous, or zigzag, from about a quarter of an inch to as much as an inch or more in length. The entrance is marked by a slight elevation, the closed end by a tiny grayish, yellowish, or whitish speck that indicates the spot where the female has come to rest. In addition to the burrows there are usually one or several vesicles, or blisters, about the size of a pea, filled with a watery fluid and situated near the burrows, generally at one end.

In a paper on these little blisters Dr. Douglass W. Montgomery has described them with all the enthusiasm of the real connoisseur: "There is no more beautiful lesion in dermatology than the pearly vesicle of scabies. When perfect it is a droplet of clear

serum shining in the skin without any symptom of inflammation whatever." A secretion from the mouth of the acarus, he continues, causes the exudation of this serum, an aliment that she absorbs through her thin and delicate skin, which allows its passage and that of air as well. It takes some time for a vesicle to form, and during this period the mite advances beyond it.

For the characteristic abnormalities so far described the acarus alone is responsible through the irritation that it sets up in the skin. The remaining changes, and they are many, must be charged to the patient himself. The surface of the skin is the habitat of various pus-forming bacteria, which penetrate through the abrasions produced by the vigorous and uncontrollable scratching and cause the development of small abscesses, or pustules. As the old ones break and, like the scratch wounds, slowly heal, scabs and sometimes areas of pigmentation follow, and these healing lesions in combination with fresh ones and the sign manual of the acarus provide a motley picture indeed.[13] Obviously the more careless and dirty a patient is the more bacteria will there be on his skin and the more severe will be the disease.

As for the parasite itself, it is ovoid in shape and just barely visible to the naked eye as a whitish speck about one seventy-fifth of an inch in length.[8] Besides bristles and other appendages it bears a series of spines, which are so set that it cannot move backward in its burrow. The acarus belongs to an old and dishonorable family; old because the mites antedate the appearance of man on the earth by many millions of years; dishonorable because so many of them are predatory or parasitic. World-wide in distribution, they are most common in the temperate regions, where hundreds of species may be found in dead leaves; under stones and loose bark; in soil; in streams, ponds, and in the sea; in stored foods as sugar, cheese, and meat; and on various mammals and birds, for about half of the known species are parasitic.

The history of scabies contains two problems. Who first saw the itch mite, and who proved that it causes the disease?

The earliest investigator to be credited with its discovery was Aristotle, but modern medical opinion is by no means certain that

the father of biology was actually describing the acarus.[5] The next name to be mentioned is that of Zau-yun-fang, who is said to have observed early in the seventh century a burrowing mite that could be removed from the watery contents of scabietic vesicles with the point of a needle. Third on the list comes Avenzoar (1070–1162), a Moorish physician of Seville, who is now thought, however, to have been describing the body louse. A Benedictine abbess is fourth: Saint Hildegarde, Lady Superior of a convent in the Rhine country near Bingen and author of a work on pharmacy entitled *Physika* that was published about 1050–60. She wrote of "little worms which are born in human flesh" and hurt a person with their "nibbling."

But for one good reason or another Friedman passes all these candidates by in favor of At-Tabarī, an Arabian physician who lived about 970 A.D. He has been described as an outstanding practitioner, an ambitious scholar and investigator, who sought only for the truth without asking from whom it came. He was never averse to acquiring more knowledge, from experienced laymen or even from old women, which, says Friedman, probably explains his discovery of the itch mite. The seventh chapter of his ten-volume *Hippocratic Treatises* deals with scabies, and describes an animalcule that can be "removed with the point of a needle. If placed on the nail and exposed to the heat of the sun or fire, it moves. If the animalcule is crushed between the finger nails, one hears it crack." [5] Though he seems to be describing the acarus he did not refer to it as the cause of scabies, for in common with those who followed him throughout many centuries to come he had no reason to suspect its relation to the disease.

He was thoroughly under the sway of Hippocrates, according to whom four cardinal humors, or fluids, were fundamental to life: blood, the hot, moist humor; phlegm, the cold, moist one; yellow bile, hot and dry; and black bile, cold and dry. If these four essentials were properly mingled in due proportion the body remained in a state of health. But if there were any irregularity in the mixture disease made its appearance, and it is not without interest to note in passing that when we speak today of melancholy we go back about twenty-three centuries to Hippocrates,

for the term is a literal translation of two Greek words meaning black bile. Thick, dark, and acrid, this was believed to cause gloom and dejection when present in abnormal amount.

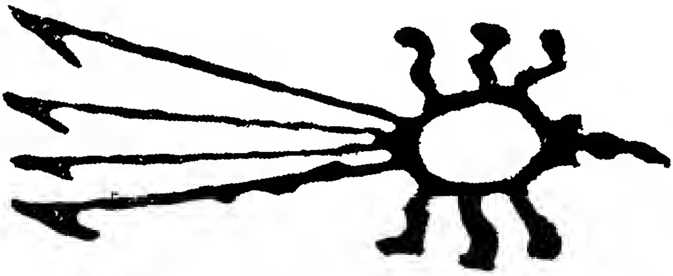
As At-Tabarī was a firm believer in the doctrine of spontaneous generation also, nothing was easier for him than to account for the origin of scabies. Obviously it must be due to the eating of "hot and dry" foods such as garlic, onions, salted fish, and "sharp" vegetables, which upset the normal balance of the four humors and caused the body to become "acrid, sharp, and viscid"—the very state necessary for spontaneous generation of the itch mite in the skin. How could it be otherwise?

This belief in the four humors ruled medicine for many hundreds of years afterward; hence when the physician encountered a disease of the skin he did not think of it as such, but immediately began to wonder what humoral, that is to say internal, disorder could possibly have caused it.

The earliest exact description of the acarus is said to have been furnished by Thomas Moffet, an English physician, though naturally he was limited to what could be seen with the magnifying glasses of relatively low power that were available in his day. His book, primarily entomological rather than medical, appeared in Latin in 1634 and in English translation in 1658. Rondolet, an Italian, had written in 1592: "Women extract them with a needle, and so relieve themselves of the itching," and Moffet, too, is thought to have derived his information from the laity. For besides the Italian peasants those of Spain, Germany, and Corsica had long known how to remove the itch mite. As for England, it is believed that Samuel Johnson procured from a similar source the definition of the itch that appeared in his famous dictionary: "A cutaneous disease extremely contagious, which overspreads the body with small pustules filled with a thin serum, and raised as microscopes have discovered by a small animal. It is cured by sulphur." [5] Curiously enough it does not seem to have occurred to this stickler for accuracy that a pustule is filled with pus, not with serum.

The first recorded drawing of the acarus was included by August Hauptmann in a letter of February 28, 1657, to the Jesuit

Father, Athanasius Kircher, a microscopist of note.[5] Hauptmann wrote that it had a monstrous form, with many rather longish tails sticking out behind, and looked like the mites found in cheese. His drawing, says Friedman, resembles a caricature



First Recorded Drawing of the Itch Mite

rather than an attempt at exact representation, yet the four posterior bristles portrayed indicate an honest endeavor to reproduce what he was able to see. In addition to the sketch his letter carried the information that the natural baths at Wolkenstein, which contained sulphur as well as other minerals, were remedial against the itch.

It was two Italian investigators, Giovan Cosimo Bonomo, a physician, and Diacinto Cestoni, a pharmacist and naturalist, who demonstrated conclusively that scabies is caused by the itch mite, confirmed the old belief of the laity that the disease is contagious, and explained why it is so.[6] Bonomo saw the patients but Cestoni, the biologist, was better fitted to carry on a study of the organism and it was he who prepared, identified, and described it and is given the greater credit.[1, 5] With their crude microscope the two investigators studied the little animal and its habits and, finally convinced of its causal relation to the disease, communicated their results on June 20, 1687, in a letter to Francesco Redi, poet, naturalist, physician, and one of the early and most determined opponents of the doctrine of spontaneous generation. He embellished their work with literary flourishes and published it about a month later—the first scientific proof of the parasitic nature of scabies and the foundation of all modern knowledge of the dis-

order. Nay, more; the most important contribution of the seventeenth or any preceding century, for it was the first demonstration that an organism of microscopic size can cause a definite disease.

It is unfortunate that the two collaborators should have indicated so loosely the epithelial covering of the vesicle as the chief abode of the mite,[7] for their lack of precision gave rise to years of misunderstanding.[5] Bonomo credited the peasant women of Italy with showing how to catch the mite and the following excerpt from the letter, as reproduced in translation by Friedman,[6] suggests that they knew enough to look in the burrows rather than in the vesicles, where it is rarely found.

He (Cestoni) told me repeatedly that he had many many times observed that women extract, from the bodies of their children affected with scabies, a something that I do *not* know; and, by means of the point of a pin they draw these somethings out of the smallest vesicles, those which are not yet ripe or purulent. They put this unknown thing on the nail of the thumb of the left hand, and, then, with the nail of the thumb of the right hand, they crush it, and in so doing they believe they hear a little crackling sound. He (Cestoni) had seen the same thing practiced, with mutual kindness, by the slaves affected with the itch here in the galley (Bagno) of Leghorn.

A year after the publication of this letter Carolinus Musitanus, forgotten author of many and voluminous treatises on medicine and related subjects, made good the omission by explaining that the acarus is to be found at the ends of the burrows and not in the vesicles.[8] Bonomo and Cestoni must have known this, else they could not have repeatedly obtained the mite for study, but they did not record the observation; nor did any of their immediate followers save Musitanus and Joseph Adams, in 1807, in his *Observations on Morbid Poisons, Acute and Chronic.* Some of the early writers stated that it could be found in the vesicles, whereas others had said the burrows. Those who favored the watery fluid of the vesicles were wrong. The few who said it could be extracted from the burrows were right but, with the exception of Musitanus and Adams, they did not specify what part

of the burrow. Musitanus was explicit, for he wrote: "Furthermore, if you wish, you might be able, with the point of a pin, to pluck the animalcule out from the end of the burrow." [5] This is the first recorded statement of the precise location of the itch mite, in the minute whitish or pearly elevation marking the end of its tunnel. Since the peasant women were so successful in extracting it they must have known just where it was to be found, and it may very well be that Cestoni meant the ends of the burrows when he referred to the "smallest vesicles, those which are not yet ripe . . ."

Because of Bonomo and Cestoni's omission those who tried to repeat their observation failed miserably, since they examined only the vesicles; no one bothered to look in the one and only place where alone it could infallibly be found. A few naturalists and physicians had seen the acarus and even drawn it, but not really understanding where to look for it had been unable to reproduce it for the incredulous on demand. The work of Moffet and of Musitanus was overlooked or forgotten, and in the eighteenth century the old doctrines were resurrected and scabies was referred once more to "melancholic juices," "acridities," "special fermentations," and "irritating juices." Suggestions that it might be of parasitic nature were treated with polite incredulity, even though Richard Mead and others had translated the Bonomo-Cestoni letter into Latin or into English for all who would to read; and Johann Ernst Wichmann had endeavored to revive interest in the problem in 1786 with his confirmation of the Italian investigators' findings and a first attempt at experimental transmission of the disease.[5]

All to no avail. The riddle remained virtually unanswered for almost a century and a half after publication of the famous letter, and the itch mite came to be regarded as a pure figment of the imagination. Whereas its occurrence in the lesions of scabies had been a matter of common knowledge among the people of Europe for centuries, its very existence was called into question by some of the leading authorities of Paris, where the faculty of medicine still dominated medical thought and teaching in Europe, and hence throughout the world. Far into the nineteenth

century even those who admitted its existence continued to regard the presence of the acarus in scabies as a mere coincidence.[5, 7]

The last chapter in this tragedy of errors was written on August 13, 1834, when Simon François Renucci, a student at Alibert's clinic in Paris, stuck a needle into the skin of a patient suffering from scabies and withdrew a tiny ovoid body—the acarus.[5] It could be demonstrated without a magnifying glass, by the "sole help of the beautiful sunlight." Though various writers have hailed Renucci as the discoverer of the itch mite, he modestly referred to himself merely as its rediscoverer, and admitted subsequently that he had learned the trick of extracting the organism from the peasant women of his native Corsica, who were expert in that art. He showed conclusively that the acarus must be sought in the burrow and not in the vesicle, and finally succeeded in teaching the profession that he was so soon to adorn something that the people of Europe had known for 250 years.

But let us not be too severe on those physicians of a bygone day. For many years they had been blinded by the doctrine of the four humors, to which they firmly believed their observations must be adapted. The people, on the other hand, uninhibited by any traditions of the sort, could view events with the clear and impartial gaze of a child.

Thirteen years before Renucci's demonstration of the mite, J. G. A. Lugol, a distinguished physician of Paris, had inoculated the fluid from vesicles into himself and eighteen other persons, none of whom contracted scabies though the experiment was carried out with all necessary care. The outcome was regarded as decisive, and Lugol offered a prize of 300 crowns for a demonstration of the itch mite. A good loser, he arranged a dinner for a number of noteworthy guests at which the award was to be presented to Renucci. But the young student was too bashful to attend. He said that what he had done was too simple to deserve such high honor, and begged Lugol to send the money to his lodgings.[11]

X

QUININE

In the city of Lima, which is the capital of Peru, the wife of the Viceroy, at that time the Count of Cinchon (those who say it was the Marquis of Mancera are mistaken) fell sick. Her illness was the tertian fever, which in that part is by no means mild but severe and dangerous. The rumour of this illness (as generally happens to important people) which at once became known throughout the city spread to the neighbouring places and reached Loxa. Thirty or forty years have passed I think from that time until now (1663).

A Spaniard, who then held the governorship in that place, was informed about the illness of the Countess, and decided to advise her husband the Viceroy by letter. He did so and wrote that he possessed a certain remedy, which he unreservedly recommended, and if the Viceroy would use it, his wife would recover and be freed from all fever. The husband told his wife about this communication, and she immediately agreed. Then, since we readily trust that which we hope will profit us, the Viceroy ordered the man from whom he hoped for help to be summoned without delay, and he was therefore ordered to come to Lima at once, which he did. When admitted into the presence of the Viceroy he confirmed verbally what he had said in the letter, and told the Vicereine to be cheerful and confident, since he was certain she would recover, if she would stand by his advice. Having heard this she decided to take the remedy, and after having taken it, to the amazement of all, she recovered sooner than you can say it.

When this was learnt in the City, the people approached the Vicereine by intermediaries, not so much joyfully and congratulatorily, but supplicatingly, begging her to deign to help them, and say, if she would, by what remedy she had at last so marvellously, so quickly, recovered, so that they, who often suffered from precisely this fever could also provide for themselves.

The Countess at once agreed. She not only told them what the remedy was, but ordered a large quantity of it to be sent to her, to relieve the sufferings of the citizens, who often suffered from the

fever. Nor did she only order this great remedy of the Bark to be brought, but she wished to dispense it to the many sick with her own hands. And the thing turned out so well that, just as she herself had experienced the generous hands of God in that miraculous remedy, so all the needy who took it marvellously recovered their health. And this bark was afterwards called Countess's Powder, which in Spanish is *los polvos de la Condeça*.[10]

Although Alexander von Humboldt, the great traveler and naturalist, who visited Lima in 1802, thought this pretty legend apocryphal, and an article in the *Penny Cyclopaedia* suggested doubtful authenticity as early as 1837, the story long remained an integral part of the history of quinine. Not until 1941 did it finally receive the *coup de grâce*, at the hands of A. W. Haggis, from whose article on errors in the early history of cinchona the preceding quotation comes. The original account, first given out in 1663, is supposed to have been taken from a letter written in Latin by an Italian merchant of many years' residence in Peru. But neither this letter nor any further record of it is known to exist, while no other contemporary writer and not a single one among all the historians of the New World makes the slightest mention of the event. The letter omitted the first "h" in the name of the Count of Chinchon, and Linnaeus followed this spelling when he named the species of tree that provides the bark *Cinchona*, in honor of the Countess.[15]

The heroine of the story is said to have been Ana de Osorio, daughter of the Marquis of Astorga, who was married to the Count of Chinchon on August 11, 1621.[10] She died, however, on the Day of the Conception of Our Lord, 1625, or three years before the appointment of her husband, Don Luis Geronimo Fernandez de Cabrera y Bobadilla, fourth Count of Chinchon, as Viceroy of Peru. Since the legend states that he had been in office ten years at the time of his wife's illness it must have been his second wife, Francisca Henriquez de Ribera, whom he married in February, 1628, that accompanied him to Peru as Vicereine in the same year and, according to tradition, was so miraculously snatched from the edge of the grave.

But though the Count suffered almost continuously from

malaria Haggis could find no evidence to suggest that the second Countess was ever attacked. Nor is it in any way certain that she returned to Spain to distribute the remedy among the poor, as has been related. If she did, it must have been on a temporary visit, for the Archives of the Order of Franciscan Friars, in Lima, prove that she died on the way home in Colombia, then a province of Peru: "By these presents let it be known unto you how, on the 14th January of this year 1641, in the City of Carthagena of the Continent of this Kingdom, Our Lord gathered unto Himself, Donna Francisca Henriquez de Ribera, Countess of Chinchon, and a patroness of our Holy religion." [15] The evidence suggests that she was carried off by an epidemic of some sort.[10]

The history of quinine is not without other legends, though none is quite so touching. The most fantastic, perhaps, tells how the Indians learned the curative value of cinchona bark by watching mountain lions with ague eat it.[13] According to another tale, less difficult to believe, the natives first recognized its properties when an earthquake near Loxa caused some trees to fall into a lake and an Indian with fever rapidly recovered his health after having drunk of the water. Or again, two Europeans, in 1600 and in 1630, were said to have been cured of ague with cinchona bark administered by native chieftains. This story is supported by the statement of William Arrott, a Scottish surgeon who had gathered the bark in Peru: ". . . the current opinion at Loxa is, that its qualities and use were known by the Indians before any Spaniards came among them; and that it was by them applied in the cure of intermitting fevers, which are frequent over all that wet unhealthy country." [7] On the other hand, it has been said that the Indians of Peru attached no importance to the bark, and were even prejudiced against its use.

The truth of the matter is that accounts of the way in which its medicinal virtues were discovered are so conflicting that even von Humboldt himself could not unravel them.[4] He believed the most reliable to be the story that in accordance with a local custom the Jesuit missionaries in Peru had endeavored to distinguish the various kinds of trees by chewing their bark, and that

this had disclosed to them the intense bitterness of the cinchona. Those with medical training were thereupon led to try an infusion of the bark in ague, and so its power was revealed. True or not, this is the only suggestion that medicine had any hand in the discovery.

If it was not the Countess of Chinchon that introduced cinchona bark into Europe, who was this great benefactor? Here, again, utter confusion reigns. It could not have been the Count's physician, Juan de Vega, who has so often received the credit, because he never returned to Spain but remained as professor of medicine in the University of Lima.[10] The earliest reliable accounts say that the drug was producing marvelous results in Lima before 1633, and it seems highly improbable that once the value of cinchona had been recognized in South America its introduction into Europe would have been long delayed.

Sir George Baker, one of the most illustrious medical men of his day, wrote in 1785, on the authority of a letter from a Spanish physician, that Peruvian bark was first brought into Spain in 1632, but that members of his profession had been far from zealous in promoting its use. Their coldness was counteracted, however, by the enthusiasm of the Jesuits who, having received large quantities of the drug from their brethren in South America, supported it with all their great influence and took it into Italy and the Netherlands as well.

England first became acquainted with it in 1655, but for a time the physicians of London were afraid to employ it, in the belief that it was harmful and also because they could not bring themselves to prescribe a remedy that had not enjoyed the support of Galen. Although the great Sydenham shared their apprehension at first he conceived, said Baker, ". . . a higher opinion of the bark, in proportion as he advanced in age; so that, had his life been much longer continued, it seems likely that he would have divested himself of all his prejudices. . . ." As a matter of fact, he became one of the first to recognize its specific power and is credited with having introduced the method of ad-

ministering it between, instead of during, attacks. He is said to have learned this, however, from Robert Tabor,[4] an irregular practitioner, who will appear later on in this story.

Baker concluded his article in the following words:

> The imperfect sketch of history, which I have attempted to delineate, presents to the mind reflections a little humiliating to our profession. Had it not been for the casual experience of an uncivilized people, it might never have been discovered, that there existed, in the stores of nature, a specific febrifuge. Had not the influence of a great religious society, unconnected with the practice of physic, counteracted prevailing prejudices, at an early period, this medicine, though brought into Europe, might have long remained in obscurity, unknown and useless. And lastly, had not physicians been taught by a man * whom they, both abroad and at home, vilified, as an ignorant quack or empiric, we might, at this day, have had a powerful instrument in our hands, without knowing how to use it in the most effectual manner.

The man to whom Baker's footnote referred as ". . . a debauched apothecary's apprentice of Cambridge . . . most diligently imitated by our most famous physic doctors . . ." was Robert Tabor, Tabord, Talbor, or Talbot.[4] He had been fortunate enough to cure Charles II of malaria, and in consequence was appointed one of the King's Physicians-in-Ordinary and knighted in 1678, when he was but thirty-six years of age. Charles recommended him in the highest terms to Louis XIV of France when the Dauphin, his only surviving son, was seriously ill with a pernicious fever. Yet Tabor really was a quack, for he did not give a clear account of his method of prescribing cinchona bark, and intimated that it was dangerous in any other hands but his. Nevertheless, the beautiful and vivacious Madame de Sévigné, correspondent extraordinary, did not hesitate to praise him without reserve in letters to her daughter at the expense of the French physicians, describing his remedy as marvelous and the man himself as divine. And all this even though he failed to save the life of her most eminent and most intimate friend, La Rochefoucauld, whose death was ascribed to gout—for Tabor did not confine his practice to malaria.

The presence of cinchona bark in Tabor's preparation was disguised by the addition of claret, and the formula was altered from time to time in order that it might remain a secret. As the Dauphin recovered, Louis treated Tabor with the greatest consideration and begged him to remain in France, but the royal offer was refused.[13] In 1679 the King bought the famous recipe for £2,000 and had Tabor publish it. The Englishman died two years later, however, too soon to reap the reward of the publicity given his prescription, as he undoubtedly would have done had he lived. For in the words of Latham: "What Sydenham gave away, Tabor sold." [4]

The Jesuits' bark, or Jesuits' powder, as cinchona was often called, gave rise to a bitter war of words throughout Europe, due in no small degree to anti-Jesuit feeling. At last this ran so high that the drug was cried down in England by the general public as the Jesuits' poison.[5] But part of the opposition to the new remedy arose from the fact that it was sometimes ineffectual because of adulteration, a practice begun in Loxa about 1650,[13] and another part from the fact that in those days of inadequate diagnosis it was not infrequently administered for fevers that were not malarial in origin and naturally failed to cure them. Again, the bark then available differed widely in activity, some samples having been actually worthless.[16] Its favorable reception was further delayed, too, by its extreme scarcity and the high price at which it was sold. Lament was voiced that it was nowhere to be found save in the hands of the great and the opulent, who kept it for their own use and that of their friends. So high was the cost, indeed, that it was called a gift worthy of acceptance by princes, and so acute the shortage that a physician of Delft said he had a patient who was seized with an obstinate intermittent fever in February, 1658, yet could not procure bark for his relief until the following June.[2]

Despite all these handicaps the drug slowly made its way, for the world desperately needed, and had needed for centuries, a cure for its most prevalent and devastating scourge. Malaria shifted populations, made extensive regions all but uninhabitable, interfered with military campaigns, and changed the currents of history. Even today the annual number of cases is thought to be

800 million, and the annual deaths are estimated at more than three million. India suffers most severely. Seventeen of our own Southern states struggle with a relatively mild form of malaria, and its ravages in this country have been put at half a billion dollars annually. No other disease has been so fatal and so costly.[15, 16] John Bunyan's name for tuberculosis, captain of the men of death, later popularized by Osler, might better have been given to malaria instead.

Among the illustrious who fell victim to it were Alexander the Great, Oliver Cromwell, Albrecht Dürer, and Lord Byron, while those more fortunately rescued by cinchona included Louis XIV; Colbert, his great finance minister; the wife of the Dauphin; the Duke of Villeroi; Prince de Condé; and Louisa Maria, niece of Louis and Queen of Spain. The illness of the Grand Monarch has been referred to the hordes of mosquitoes in the ponds at Marley,[9] his favorite residence, and no doubt the explanation would hold for his family circle as well.

The names first applied to malaria were in part merely descriptive: "ague," from the Latin word *acutus*, sharp; "intermittent fever," because of its periodicity; "tertian," "quartan," or "quotidian" fever according to whether the attacks recurred every third day, every fourth day, or every day. But "swamp fever" was an attempt to explain its cause, for an association with marshy lands had been recognized ever since it was first suggested by Varro, a gentleman-farmer of Rome.[16] Noxious exhalations from swamps appear again in the term "malaria," coined in 1709 from two Italian words meaning bad air by Torti, it is said, one of the first physicians in Italy to prescribe cinchona. This explanation, which no doubt gave to night air its former unsavory reputation, since the malaria-bearing mosquito flies chiefly at night, prevailed until 1880. It was then that Laveran, a French army surgeon, discovered the parasite, and seventeen years later that Ronald Ross, a medical officer in the British Army, proved its transmission by mosquitoes. Yet vague foreshadowings of the real cause had been in existence ever since the great Hindu physician, Susrata, suggested a possible connection between these pests and malaria long before the fifth century of

our era.[3] To return to comparatively modern times, Baker made the curiously interesting observation in 1785 that the female servants in many English families were almost exempt from a disease that few of the male servants escaped, especially those who worked in the open air.

The introduction of cinchona ushered in a new epoch, and it has been said that the drug did for medicine as much as gunpowder had done for war. In other words, medicine was modernized. The fact that cinchona rapidly cured a fever for which older remedies had been given in vain, according to the belief that disease results from imbalance among four cardinal body fluids, gave the finishing blow to a venerable but utterly fallacious idea. Thus F. H. Garrison, in his *Introduction to the History of Medicine.*

The history of cinchona after the middle of the seventeenth century is marked by futility, extravagance, and toward 1850 by a rapidly dwindling supply. An enormous trade in the bark had developed and the trees were being ruthlessly stripped and destroyed, for although the Jesuits at Lima had insisted as early as 1640 that for every tree cut down a new one must be planted, no one paid any attention to the order and the unregulated scramble for the precious drug went recklessly on. Antonio Ulloa, said to have been an accurate chronicler, put the whole situation in a nutshell when he wrote in 1735: "Though the trees are numerous, they have an end." [16]

After it had become obvious that South American production would never keep pace with the enormous world demand, says Taylor in his history of cinchona, England and Holland determined to bring the tree from the New World and cultivate it in the Old. The first experiment, undertaken by the Dutch in 1852, led to virtually nothing for it had not yet been fully recognized which species and varieties were valuable and which worthless. In the meantime, Clements R. Markham, who was neither a botanist nor a horticulturist though he had considerable knowledge of South America, had been sent there in 1859 by the British Government, together with a company of gardeners and bota-

nists. Introduction of the trees into British India and Ceylon was a failure, however, like the first Dutch attempt, because the species chosen by the expedition did not yield enough active bark to pay for its cultivation. By 1864 no planter in his right mind would even consider growing cinchona, for there appeared to be no hope of profit in such a venture.

But another Englishman, resident in South America, was soon to change the whole future of the tree, and the way in which he did so is described as the most fortuitous event in the colorful and all but incredible history of quinine.[16] Charles Ledger had lived for years on the shore of Lake Titicaca, which divides Peru and Bolivia, and thus not far from the district that had always provided the best barks. An Indian servant whom he sent to gather seed brought back fourteen pounds from what was presumably *Cinchona calisaya*, known for years as the most valuable species, and this package settled for all time the question whether the world was to be supplied with quinine by the British or the Dutch.

Ledger sent the seed to his brother George, in London, with the request that they be offered to the British Government for planting in India. The offer was declined, however, and George Ledger, knowing that the seed would not retain indefinitely the power of germination, offered them to the Dutch Government for its plantations in Java. One pound was bought for the equivalent of about $20, and a promise of further payment was made if the seeds germinated. Soon afterward the Netherlands Government paid Charles Ledger something over $100, later an additional sum equal to almost $500, and upon his retirement in 1895 granted him an annual pension of the same amount.

George Ledger went back to London with the remaining thirteen pounds of seed and literally hawked them about the streets. Finally he arranged with a planter who was home from India on vacation to buy them, and eventually these seed were planted in India. But there they failed to germinate, or those that did never reached productive capacity.

The single pound that arrived in Java in December, 1865, was in large part spoiled, but the good seed were carefully sorted out and planted and about twenty thousand germinated. Twelve

thousand of these seedlings were set out in a nursery bed the following year, but no locality could have been worse for *Cinchona ledgeriana*, as the plants were subsequently christened. Java had hundreds of thousands of cinchonas, many of which were flowering and none of which were of much value, and the trees are given to hybridizing because their pistils of different length prevent self-pollination and ensure cross-pollination. Thus it was to a society of plant mongrels that *C. ledgeriana* was introduced, and its pollution by foreign pollen was not only likely but inevitable unless some method of prevention could be worked out.

Purity was maintained by selection of the trees that provided the highest yield of quinine, and their segregation at such a distance from other cinchona plantations that insects would be unable to cross-pollinate the selected stock. But it turned out to be a difficult tree to grow. After many years of trial and error it was found to prefer an elevation between 3,000 and 7,000 feet, just south of the Equator, and to need an adequate rainfall, which must be evenly distributed with no dry season longer than one month in duration. The temperature range is also of importance, for young trees are immediately killed by frost and older ones will tolerate but little. The soil must be reasonably porous. In such a mountainous region as Java it is not easy to find the necessary flat or gently sloping land; hence series of terraces must be constructed to prevent erosion, a procedure that calls for both money and a high degree of skill. Another disadvantage of cinchona cultivation is the long period that elapses before a profitable yield of quinine can be secured, for not until the trees are from fifteen to eighteen years old do they come into full bearing. Finally, as they are difficult to grow on their own roots once the soil of virgin forest sites has become exhausted, the modern custom is to graft them on *C. succirubra*.

C. ledgeriana is a medium-sized tree belonging to a family that includes coffee, ipecac, and the gardenia. In fourteen years it reaches a height of about thirty feet, and seventy-five to eighty feet after forty-five years. Its leaves are perfectly smooth and more or less elliptical in shape, its cream-colored, lilac-like flower clusters deliciously scented and sometimes almost feath-

ery, its seeds so minute that a single ounce would contain about ninety-eight thousand. These tiny and delicate seed introduce other difficulties in addition to those already mentioned.

At such trouble and expense is the world furnished with quinine! Prescribed by the grain, Taylor continues, it is produced by the ton—from 650 to 750 tons annually in normal times. The Dutch have been accused of trying to monopolize the industry, but although much labor and time had been spent on its Javanese plantations the Netherlands Indies Government freely sold or gave away its seed. Even after the burden of cultivation had been assumed by private planters the cost of a five-day treatment for malaria was less than that of admission to a good movie today. Impoverished populations admittedly cannot afford quinine, but neither can they buy many other necessities and their inability to purchase the drug is hardly a valid criticism of the industry.

Despite their wide and generous distribution of the seed there has been no success equal to that of the Dutch, perhaps because the necessary combination of science and patient skill has been lacking.

Though *C. ledgeriana* eventually yields generous amounts of quinine, it is notably deficient, unlike *C. succirubra*, in the three other principal cinchona alkaloids—quinidine, cinchonine, and cinchonidine. Hence planters maintain small acreages of the latter tree for the sake of these, which are effective against malaria though not so actively as quinine. Fortunately it is possible to extract them all by a relatively simple procedure, and the mixture is called totaquine or, since it costs only about one sixth as much as quinine itself, poor man's quinine.

Quinidine is of special interest to us because an important use for it was found through a layman.[8] Wenckebach, the famous Viennese heart specialist, was informed by a patient in 1914 that he had been able for years to stop his attacks of rapid and irregular heart beat, or auricular fibrillation, with quinine. Four years later another cardiologist, Frey, discovered that quinidine is even more effective than quinine in restoring the normal rhythm of the heart.

Because of the relatively high cost of quinine, no less than the difficulties encountered in maintaining an adequate supply for the world, and because the chemist is never happy until he can make something out of something else, attempts to synthesize this invaluable drug have been in progress ever since the eighteen-year-old English chemist, William Henry Perkin, tried to prepare it in 1856. He failed, but out of his experiment came the first artificial dye, aniline purple, or mauve, and eventually the great aniline dye industry together with useful drugs by the dozen. Others were as unfortunate as he in the endeavor until 1944, when two young American chemists, R. B. Woodward and W. E. Doering, were able to report success. It is no disparagement of their brilliant discovery to say that it did not bring the industrial manufacture of quinine much closer, for the process was long and tedious and the yield so small that the cost of preparation on a large scale would be prohibitive today. Still, the longest journey begins with one step, says the proverb, and there is every reason to hope that the process will eventually be simplified and made less expensive, as has been the case with so many other medicaments.

In the years that intervened between failure and success efforts innumerable to prepare a substitute for quinine were under way, and exertions were redoubled when the Germans invaded Holland in 1940, seizing all the bark in stock there, and the Japanese occupied Java in 1942 and took possession of its great cinchona plantations. Out of those years of feverish investigation have come such drugs as quinacrine hydrochloride, chloroquine, pamaquine, pentaquine, paludrine, and other compounds, each valuable in one way or another but none perfect. One upsets the stomach, for example; another is not thoroughly effective against all four species of plasmodium responsible for malaria, though perhaps this would be almost too much to expect, since even quinine itself is not; another is so poisonous that the curative dose closely approaches the toxic dose; still another will attack the parasites that live in and destroy the red blood corpuscles, but not those that are now believed to inhabit other cells of the body; and

so on.[14] Perhaps the ultimate solution will turn out to be a combination of remedies.

Hand in hand with the attempt to cure malaria have gone efforts to control it.[16] The International Health Division of the Rockefeller Foundation has established stations throughout the world where as many mosquitoes as possible are destroyed by drainage, the spreading of chemicals, and other means, and the military forces carried out an active campaign of similar kind during the late war. Control measures such as these are far more practical than the impossible task of trying to eradicate the disease. This would require the destruction of every single mosquito of the species that carries it, for the only way to break the life cycle of the plasmodium is to eliminate one of its hosts—either the mosquito or, as the young student quoted by Taylor suggested, the human race itself.

XI

PHAGOCYTOSIS

Elie Metchnikoff, one of the world's great biologists, never owned a gold watch or, indeed, any object of no special use. Not that he was unable to afford such minor indulgences, but because he disliked luxury in all its forms. His only means of self-gratification was to bring happiness to others.

In the preface to his biography by Madame Olga Metchnikoff, Sir Ray Lankester, famous biologist and intimate friend, described the great man as generous, affectionate, truly considerate of others, and a practical idealist. Yet wishing, no doubt, to portray him with all his warts, as Oliver Cromwell wished to be painted, he went on to say that Metchnikoff was emotional, impulsive, and easily moved to explosive wrath in the face of disloyalty or careless work.

A sheep in wolf's clothing!

Metchnikoff was born in a remote part of Little Russia near the town of Kharkoff on May 16, 1845. From earliest boyhood he was passionately interested in natural history, and when he was but eight years old used to offer all his pocket money to his brothers and other children as an inducement to attend the lectures that he wished to deliver before them.

When he entered the lycée in Kharkoff at the age of eleven he was still so immersed in natural science, and especially in botany and geology, that he became completely specialized by the time he had reached fifteen. A hard worker, his only recreations were debates on abstract subjects, and music, though here as a listener rather than a performer. After having been graduated he entered Kharkoff University, where he completed the four-year course in two years, and then went abroad to study in various European cities—Giessen, Naples, and Munich.

In Giessen, in 1865, he discovered intracellular digestion in a

small flatworm. It had long been known that unicellular organisms such as the amoeba take up and digest particles of food, differing in this respect from the higher animals, where digestion is extracellular, since it is accomplished outside the cells by ferments given off from them. He did not grasp at once the significance of his observation that certain tissue cells in a multicellular animal are adapted to intracellular digestion, though together with his subsequent investigations on this primitive function it gradually prepared his mind for conception of the phagocytic hypothesis.

Upon his return to Russia he received an appointment as docent at Odessa University, where his third-year students were all older than he, who was but twenty-two at the time. Before long he resigned to become professor at St. Petersburg, but conditions turned out to be highly unsatisfactory, for he had no proper laboratory and had to work between two specimen cases in an unheated museum.

In St. Petersburg he became engaged to a delicate girl named Ludmilla Fedorovitch, whom he described in a letter to his mother as of about his own age, a little over twenty-three; not bad looking, though with a complexion that was not pretty; too placid, but extremely kind and good natured, and without a vulgar trait in her character. From a prospective bridegroom an unusual letter, surely, in which the lover appears to have been lost in the scientific observer. Yet she soothed his high-strung nature, he said in conclusion, and he was becoming more fond of her every day.

Their happiness seemed assured, but fate decreed otherwise. The girl's health was not improving; on the contrary, her supposed bronchitis, which almost certainly must have been tuberculosis, was growing worse with each succeeding day. Too weak and too breathless to walk as far as the church for her wedding, she was carried in a chair. An hourly struggle with disease followed, until the young husband was compelled to obtain leave from the University and take her south. On the way she suffered a pulmonary hemorrhage, and although some slight temporary

improvement set in afterward no treatment and no locality gave her permanent relief. During the period of betterment Metchnikoff had been able to return to his classes but one day, just before a lecture, was summoned to Madeira where he found his wife dying. The end came on April 20, 1873, about five years after their marriage.

By now Metchnikoff had become a complete pessimist. Working as best he could in an atmosphere of quarrels and political intrigues, in poor health, and worried over a weakness of his eyes, he spoke continually of the disharmonies of human nature and declared it an enormous wrong to bring a child into the world. Why go on living under such deplorable conditions, bereft of wife and possibly of eyesight too? He took an enormous dose of morphine, but failed in his attempt at suicide because he did not know that large amounts induce vomiting and so eliminate the poison.

During his widowerhood he continued his lectures at Odessa University, whither he had returned in 1870 as professor of zoology, though he was in a highly irritable state and driven frantic by noise in particular. As luck would have it there lived on the floor above his a family with many children that wakened him every day by their noise, and when his patience had finally reached the breaking point he climbed the stairs to remonstrate. Not long afterward, having learned that one of the children, Olga, was deeply interested in natural history, he offered to teach her. The consent of the parents was obtained and lessons were begun, but the course turned out to be a short one for he fell in love with his pupil and soon asked for her hand in marriage. She has thus described her reaction to the proposal:

> I had not suspected my Professor's feelings towards me, and was deeply moved when I was told of them; it seemed to me impossible to understand that this superior, this learned man could wish to marry a little girl like myself! . . . However, I had a great affection and admiration for Elie . . .
>
> Moreover, my young imagination was impressed by his sad his-

tory and his interesting appearance, at that time not unlike a figure of Christ . . . but I was not yet ripe for matrimony and was somewhat thrown off my balance by the unexpectedness of the event.

The persistent lover, who seemed to her so old and so wise though he was not yet thirty, overcame all her indecision at last and they were married in February, 1875. A few hours before the ceremony Olga's brothers appeared with a sled, offering her one last ride because that evening she would be a "grown-up" lady and could not play with them any more. When the mother found them thus employed she warned Olga that it was high time to dress and do her hair, and the wedding gown that she then put on was the first long dress that the girl had ever worn. However, the account gives no hint as to her exact age.

The newly married couple remained in Odessa until early in the year 1881, when Elie resigned his chair because of the depressing atmosphere at the University. They went to stay with her parents at Kieff and within two years, after Olga's father and mother had died, Metchnikoff assumed responsibility for the care of his wife's brothers and sisters.

Four years previously he had experienced symptoms of cardiac trouble and a long period of poor health now set in, aggravated by anxiety over the condition of his wife, who had a dangerous attack of typhoid fever in 1880. At last he fell into such a depression that he resolved once more to put an end to his life, and in order to spare his family the sorrow of an obvious suicide inoculated himself with relapsing fever. Scientist to the last, he chose this disease to find out whether it could be transferred by way of the blood stream. The experiment succeeded but the attempt at self-destruction did not, for although he became seriously ill he recovered in the end. An acute inflammation of the eye developed as an unpleasant sequel, but fortunately this disappeared in due course and he never had trouble with his vision again.

In the autumn of 1882, after his second attempt at suicide, Metchnikoff went to Messina for research, taking with him his wife and her two sisters and three brothers, all younger than she; for her parents had left sufficient means to assure the family of

independence. He became very fond of the children as they of him and, warmed by his kindly indulgence, they went to "the Prophet" for everything. The nickname was derived from Ilia, the Russian form of Elijah under which he was christened but later changed to the French version, Elie. At Messina the family settled in a suburb, taking a small apartment with a garden and a superb view of the sea. Of the years spent there he wrote long afterward:

"Thus it was in Messina that the great event of my scientific life took place. A zoologist until then, I suddenly became a pathologist. I entered into a new road in which my later activity was to be exerted." This great event he described in the following words:

One day when the whole family had gone to the circus to see some extraordinary performing apes, I remained alone with my microscope, observing the life in the mobile cells of a transparent star-fish larva, when a new thought suddenly flashed across my brain. It struck me that similar cells might serve in the defence of the organism against intruders. Feeling that there was something in this of surpassing interest, I felt so excited that I began striding up and down the room and even went to the seashore in order to collect my thoughts.

I said to myself that, if my supposition was true, a splinter introduced into the body of a star-fish larva, devoid of blood-vessels or of a nervous system, should soon be surrounded by mobile cells as is to be observed in a man who runs a splinter into his finger. This was no sooner said than done.

There was a small garden to our dwelling, in which we had a few days previously organised a "Christmas tree" for the children on a little tangerine tree; I fetched from it a few rose thorns and introduced them at once under the skin of some beautiful star-fish larvae as transparent as water.

I was too excited to sleep that night in the expectation of the result of my experiment, and very early the next morning I ascertained that it had fully succeeded.

That experiment formed the basis of the phagocyte theory, to the development of which I devoted the next twenty-five years of my life.

Metchnikoff was struck by the similarity between what he had observed and the escape of white blood cells from the vessels that even then was known to occur during inflammation in animals provided with a vascular and a nervous system. Immediately it occurred to him that these white cells, or leucocytes, must destroy bacteria by taking them up and digesting them. Almost twenty years previously he had discovered intracellular digestion in cells of another type, and now asked himself whether inflammation might not be a protective reaction. It is true that the leucocytes had already been suggested by two investigators as a means of defense, but the idea was original with Metchnikoff nevertheless, for he did not know this at the time and in any case no experimental evidence had been offered to support the proposal.

He was much encouraged by the great Virchow, father of cellular pathology, who had introduced the concept of the body as a cell state in which every cell is a citizen. The German happened to pass through Messina at the time, and went to see Metchnikoff's preparations and experiments. Though they seemed entirely conclusive, Virchow urged him to proceed with the utmost care in their interpretation since his hypothesis was exactly opposite to that held at the time. This taught that the leucocytes, far from destroying bacteria, furnish a medium favorable for their growth and, after having engulfed them, might actually spread disease by carrying them to remote parts of the body.

On the way back to Russia Metchnikoff stopped in Vienna to see Claus, a professor of zoology there. The new idea was explained to him and to other colleagues present, all of whom became deeply interested, and when asked for a Greek term equivalent to "eating cells" they suggested phagocytes.

Continuing his investigations at home, Metchnikoff found that during transformation of the larvae of certain marine animals the parts that atrophy are ingested by mobile cells from the mesoderm, middle of the three germ layers in the embryo, and was overjoyed to discover an example of "physiological inflammation"; that is to say, of "inflammation" occurring under normal conditions. Furthermore, he observed that in the atrophy of the tadpole's tail during metamorphosis into a frog certain cells

from the muscular tissues act in the capacity of phagocytes; in this way he learned that other mesodermal cells besides the white blood corpuscles can assume the role of destroyers.

In the autumn of 1883 he read his first paper on phagocytosis before a congress of naturalists and physicians at Odessa, in which he compared the phagocytes to an army hurling itself upon an enemy. In later years articles written by others for popular consumption often referred to the phagocytes as "policemen of the blood."

In that paper, and from that moment onward, a trend toward optimism began to be apparent in this former convinced pessimist. The discovery that the phagocytic reaction is a protective one had made the first breach in his dark philosophy, for at last he had found a salutary influence to compensate for the disharmonies in human nature. In 1907 he published his *Optimistic Essays*, which must have surprised those who knew him in youth.

So far his concept was a mere hypothesis rather than a theory, since he had not yet observed the reaction in disease. Knowing nothing of bacteriology, he cast about until he found a small transparent organism, the daphnia, or water-flea, that was subject to infection by a yeast-like parasite, a fungus, whose spores, shaped like needles and introduced with the food, penetrated the walls of the digestive tract and reached the general cavity of the body. There he saw them immediately attacked by phagocytes and engulfed. If the defenders succeeded in digesting the invaders the little creature recovered; if not, the spores developed into a fungus that invaded and killed it.

Now nothing would do but he must study the reaction of higher animals to disease, for until then he had investigated only the fixed tissues in organisms that lack a fluid, circulating tissue: the blood. The microbe best known at the time was the bacillus of anthrax, which was accordingly chosen for his experiments. First he observed that phagocytosis differed with the virulence of the infecting microbes, for whereas highly destructive ones were not attacked, weaker bacilli were promptly taken up and digested. Next he encountered active phagocytosis in resistant animals but

none in susceptible ones, and thus came face to face with the problem of immunity.

As a result of Pasteur's conquest of rabies an institute was opened at Odessa in 1886 to carry out his treatment, and Metchnikoff was appointed its scientific director. But the local physicians were hostile to its work and quarrels arose among his subordinates so, seeing that it was impossible for a layman to manage an institute with a medical staff, Metchnikoff determined to look abroad for a laboratory in which to work. Conditions in Russia were far from favorable to his scientific activities, he had severed connections with Odessa University, and his other ties with the mother country had gradually loosened. After having decided against Wiesbaden and Munich he went to Paris and called on Pasteur. Of this first interview he wrote:

On arriving at the laboratory . . . I saw an old man, rather undersized, with a left hemiplegia [Pasteur had suffered a stroke twenty years previously and one side was paralyzed in consequence], very piercing grey eyes, a short beard and moustache and slightly grey hair, covered by a black skull-cap. His pale and sickly complexion and tired look betokened a man who was not likely to live many more years. He received me very kindly, and immediately spoke to me of the question which interested me most, the struggle of the organism against microbes.

"I at once placed myself on your side," he told me, "for I have for many years been struck by the struggle between the divers microorganisms which I have had occasion to observe. I believe you are on the right road."

Despite his appearance of illness, Pasteur lived for seven years after this interview.

At once he offered his visitor a whole laboratory in the new Institute then being built in the rue Dutot; the tender was gladly accepted, and after having wound up his affairs in Odessa the new guest arrived on October 15, 1888. Eventually he was assigned two rooms on the second floor, his wife served as his assistant, and at last he was supremely happy. Now he could work in peace,

freed, as he said, from all politics and other obstacles "from above, from below, and from all sides."

His manner and appearance at about this time have been described as typically Slavonic. His hair was long and, when experiments were especially interesting, his beard neglected. No matter what the weather he appeared with overshoes and umbrella, the pockets of his overcoat bursting with pamphlets. He always wore the same hat and when excited or absent-minded, as he often was, used to sit on it.

France became for him a second motherland, and whenever he was invited in later years to leave the Pasteur Institute for laboratories in other countries his invariable reply was that he would leave it for one place only—the neighboring cemetery of Montparnasse.

By 1892 his views on the significance of phagocytosis in disease were firmly established, and he published his *Comparative Pathology of Inflammation*, while about a decade later came his chief work: *Immunity in Infective Diseases*. In cooperation with Emile Roux he discovered in 1903 that syphilis can be transferred to apes, an enormous advance in the study of this disease; and in 1906, again with Roux, that it can be prevented by rubbing calomel ointment into the infected area, provided the application be started within a few hours after exposure.

In 1908 he and Paul Ehrlich received jointly the Nobel Prize in medicine for their investigations on immunity.

Metchnikoff's association with the Institute was beautifully expressed by Roux on the occasion of his Russian collaborator's seventieth birthday, May 16, 1915. After having said that it was so painful to Metchnikoff not to give of his help and his time that he would rather be exploited than close his hand, Roux ended his speech thus:

> The Pasteur Institute owes you much; you have brought to it the prestige of your renown, and by your work and that of your pupils you have greatly contributed to its glory. You have given a noble example of disinterestedness by refusing any salary in those years when the budget was balanced with difficulty and by preferring to the glorious and lucrative situations that were offered to you the

modest life of this house. Still a Russian by nationality, you have become French by your choice, and you contracted a Franco-Russian alliance with the Pasteur Institute long before the diplomats thought of it.

New ideas, like new shoes, are uncomfortable, and not everyone finds it easy to adapt his head to the one or his feet to the other. Metchnikoff's concept of the important role played by the phagocytes in protecting the body against disease was freely accepted in France and in England. Joseph Baron Lister, first to apply Pasteur's theory of infection to surgery, gladly welcomed the view of the Russian investigator, and later said of it in a presidential address: "If ever there has been a romantic chapter in the history of pathology, it is the story of phagocytosis." [5] In Germany, on the other hand, the new hypothesis met with some bitter opposition and even Robert Koch, discoverer of the tubercle bacillus, fought against it. Many were less generous than Rudolf Virchow, who deserves special credit because it was in direct contradiction with the idea that he himself held and taught. Among the antagonists of Metchnikoff's opinion not a few contended that the determining factor in disease is not the phagocyte but the body fluids; phagocytosis, it was asserted, merely removes dead bacteria after the issue has already been decided.[8]

Now the cellular and humoral hypotheses were drawn up in battle array and the conflict went on for years, first one side and then the other appearing to be in the ascendant. It had been known since 1874 that the body fluids, or humors as the old physiology called them, and the blood in particular, exert some sort of protective action against bacteria, and the humoral hypothesis was to gain imposing support as the years went by. Thus it was shown in 1890 that even after serum, the watery portion remaining after the blood has clotted, has been freed entirely of cells it can still counteract toxic substances liberated by the organisms of lockjaw and diphtheria.[1] These newly discovered protective agents were fittingly named antitoxins, because they work against toxins; but not, be it noted, against the bacteria that elaborate and release them.

The first diphtheria antitoxin to be employed was serum from a sheep that had been immunized with small doses of the bacteria causing the disease in question.[7] After a long series of experiments on guinea pigs had shown this preparation to be curative and entirely harmless, it was tried on a human patient in von Bergmann's clinic at Berlin in the year 1891. Dr. Geissler gave the injection to a child who was gravely ill with diphtheria and, appropriately enough, the treatment was administered at Christmas time. Wernicke, who had taken an active part in all this work and is responsible for the report, did not describe the outcome, but it may be supposed that the result confirmed the experiments on animals; otherwise, no doubt, he would have recorded failure.

The statement that the body can protect itself against the soluble poisons of bacteria without benefit of cells was a heavy blow to Metchnikoff's hypothesis, but far worse was soon to come. Only four years later it was reported that the bacilli of cholera are themselves dissolved by the body fluids, with no apparent intervention by the cells.[1] The humoral hypothesis seemed even more safely ensconced.

Poor Metchnikoff turned this way and that, making one experiment after another in the hope of arriving at the truth. Not of proving himself right, look you; he was far too great a man for that. Finally he came to the conclusion that the protective agents in the body fluids, the antibodies, as they are called, are probably elaborated by the phagocytes as a result of the ingestion of bacteria or their soluble poisons.[4] This reconciliation of the cellular with the humoral hypothesis, already foreshadowed about 1890 by another investigator, was further supported by the discovery that dog serum is less destructive to bacteria than is the whole blood. When its leucocytes had been removed the blood was found to have lost a considerable amount of its protective faculty.[1]

Reconciliation was advanced again by the work of Sir Almroth E. Wright and his school, who demonstrated in 1903 that certain substances in the blood serum alter microbes in such a way that they easily fall prey to the leucocytes. These unknown agents they called opsonins, from a Greek word meaning "I prepare

food for," picturing them as a kind of sauce that made bacteria more palatable to the white blood cells. Though the work of this group did not turn out to be so useful from the standpoint of treatment as had once been hoped, it did produce invaluable results in the field of prevention. Typhoid fever, at one time more dangerous to armies than the missiles of the enemy, was virtually eliminated as a military disease by immunization with dead typhoid bacilli.

By the end of the nineteenth century it had been realized that both cells and fluids are engaged in protecting the body against bacterial invasion, and also that the problem is much more complicated than had at first been thought. The situation has been somewhat simplified, perhaps, by abandonment of the original idea that there are various kinds of antibodies. It is now suggested that the opsonins and others like the agglutinins, which cause bacteria to clump before they are finally destroyed, or the lysins, which dissolve them, may be only different phases of one single protective humoral medium.[3]

At present the situation is pictured about as follows. When bacteria or other foreign particles gain access to the body they are immediately set upon and engulfed and digested, if possible, by two kinds of phagocytes, its main defensive mechanism. Polymorphonuclear leucocytes emerge from the neighboring blood vessels and rapidly collect at the site of injury. Smallest of the protectors, these enjoy the longest name, given them because their nuclei are of such varied shape. On account of their relatively small size Metchnikoff called them *microphages*, or "small eaters"; those that perish in the conflict become pus cells.

Following in the train of the microphages come the "large eaters," the macrophages, cells with roundish nuclei and of more considerable size that wander in from the blood or other tissues or happen to be already on or near the field of battle. These constitute the reticuloendothelial system; poorly named, since it is neither a reticulum, or network; nor composed entirely of endothelium, the cells lining the blood and lymph channels; no, not even a system. But however this may be, it is now considered

probable that the cells in question give rise to the antibodies, which are antagonistic to foreign agents such as toxins or the bacteria producing them.

Thus Metchnikoff was right in his conclusion that invading bacteria are met and overcome if possible by the phagocytes, the most essential part of the defensive mechanism; and probably right in his suggestion that the protective agents in the body fluids are provided by these guardian cells.

But in the words of the Oriental proverb, even the monkey falls sometimes, and in another aspect of his work Metchnikoff went widely astray.

In certain countries where fermented milk, the yoghurt of central Europe, for example, or the kumiss of Russia, has been an important part of the diet for years, the people are noted for their longevity. Hence he conceived the idea that there is an important connection between length of life and the bacterial content of the intestine, senility being due to chronic poisoning of the body cells by microbes inhabiting this tract.[4] He therefore prescribed a diet for himself from which raw food was excluded in order to prevent the introduction of bacteria that might be harmful. As the putrefying organisms that he incriminated can live only in an alkaline medium, such as that provided by the intestinal juices, he drank milk fermented by cultures of certain bacilli that produce large amounts of lactic acid. He favored the *Lactobacillus bulgaricus* and advised implanting it in the intestine, but the attempt failed because this organism proved unable to establish itself there; hence fermented milk had to be consumed daily.

Under the new regimen his health improved, friends followed his example, some doctors recommended the beverage, and the custom spread. In this country the *Lactobacillus acidophilus* was preferred, because it will flourish in the lower intestine if large amounts of milk sugar for its sustenance be taken in addition.[2] Fermented milk under various names was served at every soda fountain in the land, and its consumption soon became a veritable fad. No miraculous results were reported, however, and there

are grave doubts today whether this drink exerts any beneficial effect at all. There must have been something wrong with the hypothesis!

In any case it landed Metchnikoff in hot water. As the notion of the hygienic value of fermented milk began to spread, a manufacturer who wished to exploit its possibilities by organizing a company for its distribution asked him to recommend a man trained in its preparation.[4] Anxious to find a position for a young protégé, Metchnikoff did so. Then the manufacturer declared that he could not be sure of success without the guarantee of Metchnikoff's name, and after consultation with the legal adviser of the Pasteur Institute the necessary consent was given. The formula agreed upon was: "Sole provider of Professor Metchnikoff."

As a consequence of his generous act Metchnikoff was derided, bitterly attacked, and accused of having entertained the very lowest of low commercial motives. Yet wholly without justice, for Madame Metchnikoff, who surely knew better than anyone else, declared that he never made one single penny from the enterprise, nor ever wished to do so.

Upon the arrival of his seventieth birthday Metchnikoff was greatly changed. His hair was whiter, his figure bent, his movements slow. Since the autumn of 1913 he had passed through several alarming heart attacks, and was crushed besides by the outbreak of war in the summer of 1914 with the consequent disorganization of his beloved Institute. Nevertheless, a sort of temporary rejuvenation set in on the great day, and he was more animated and happy than he had been for a long time. But early in December, 1915, there was a distinct change for the worse, and it became only too obvious that the end was approaching. He had repeated and severe episodes of heart failure; fluid collected in his chest, his abdomen, and his legs; he was confined to bed; and was unable to sleep without the assistance of an opiate.

Perhaps to reassure his wife he professed to be wholly unafraid of death, saying over and over again that it was a natural event and that he was ready. But "Men feare *Death* as Children

feare to goe in the dark. . . ." and of her who watched so faithfully at his bedside he asked: "You will hold my hand when the moment comes?" Then suddenly, in the late afternoon of July 16, 1916, he was gone.

XII

X RAYS

THE reddish glow of the neon tubes that are used so widely for advertisement and display is no novelty at the present time. But toward the close of the nineteenth century the phenomena taking place in their ancestors, tubes in which electricity was discharged at high voltages through rarefied gases, had become a matter of real concern to the physicist.

About 1855 Heinrich Geissler, a glass blower at the University of Bonn, had constructed tubes that contained various gases at low pressure and showed a beautiful soft glow when a high-tension electric discharge was passed through them. The color of the light depended upon the gas employed and the degree to which it had been exhausted. Several decades later Sir William Crookes, the celebrated English chemist, developed a tube with a much higher vacuum, and showed by his experiments that what had until then been called cathode rays are not rays at all but a stream of electrons, or particles of negative electricity.

Much of this earlier work was repeated by Wilhelm Conrad Roentgen, then professor of physics at the University of Würzburg, with a result that all the world knows. Seldom, perhaps never, has a scientific discovery aroused such a storm of interest, favorable and unfavorable, as that of the X rays in 1895. Indeed, Roentgen could have said with Lord Byron: "I awoke one morning and found myself famous."

Wilhelm, the only child of Friedrich Conrad Roentgen and Charlotte, his wife, was born on March 27, 1845, in a gray frame and slate house in Lennep, a small provincial town in the pleasant rolling country bordering on the Ruhr.[3] His father was a prosperous textile merchant and most of his forebears had been artisans or small businessmen, though there had been some notable

musicians and a gifted engineer who ran the first steamboat on the Rhine. His mother, whose maiden name was Frowein, came from a family of successful merchants. Thus the background of the new arrival was on the whole one of industry and pride in honest work but otherwise unpretentious, and he turned out to be a sport—in the sense of the geneticist, of course: a sudden deviation from type.

When Wilhelm was about three years old his family moved from Lennep to Apeldoorn, Holland, whether or not as a consequence of the Revolution of 1848 is unknown. In any case, they became Dutch citizens within a few months.

As the only child of a conservative and well-to-do merchant the boy had a calm and pleasant childhood, but his schooling was informal from the first. He attended primary and secondary public schools in Apeldoorn and then a private boarding school, but after that the record is silent until December, 1862, when he was registered at a technical school in Utrecht that prepared students for entry into a higher institution of technology but not for a university. Here he took courses in algebra, geometry, physics, chemistry, and applied science but proved to be only an average student, preferring to spend his time in skating, riding, making mechanical contrivances, or roaming about the countryside.

It happened one day that a fellow student had drawn a caricature of an unpopular teacher on a firescreen in the schoolroom, and Wilhelm was enjoying it to the full when the instructor himself entered. In a towering rage he demanded the name of the offending artist, but the boy would not reveal it. The director of the institution was accordingly summoned and, in order to pacify the angry teacher, he ordered that Wilhelm be expelled.

Though only a few members of the Roentgen family had received a university training, and Friedrich secretly hoped that Wilhelm would succeed to his business as a merchant, he thought it important nevertheless that his son be equipped to enter a profession. He thereupon set about obtaining permission for a private examination that would furnish the credentials necessary for entrance to college and the youth spent almost a year in preparing himself, notably by adding Latin and Greek to his studies.

But ill luck continued to dog his footsteps. On the day before the test the examiner, who was favorably disposed toward him, was suddenly taken ill and replaced by a teacher who had participated in the expulsion proceedings. The result was Wilhelm's failure.

In order to achieve at least some degree of higher learning he registered next as a special student in the University of Utrecht, where for two semesters he attended lectures on physics, chemistry, zoology, and botany. Then, hearing that the Zürich Polytechnic School accepted students who lacked the usual credentials provided they could pass the difficult entrance examination, he made application at once. When he arrived, on November 16, 1865, he carried with him a letter from his physician explaining that he had been under treatment for an eye trouble. This, in addition to the fact that he was twenty, or two years older than the average student, and able to present good reports from the Utrecht schools in mathematics especially, prompted the authorities to be lenient and accept him without the examination as in good standing.

For three years he studied mathematics, technical drawing, metallurgy, hydrology, thermodynamics, and many other branches of mechanical engineering. Now his work was excellent, but he became more and more interested in the basic sciences though the idea of specializing in one of them had not yet occurred to him. He took but one course in physics, and that was of a technical nature. Roentgen, the great experimental physicist, never had a fundamental course in experimental physics during his years in college!

After having been graduated in engineering he stayed on at the school to continue his studies in mathematics and to attend lectures on the theory of light. His experiments on the physical properties of gases were begun, and as they progressed he gradually came to realize that this was the sort of investigation to which he was best suited. On June 22, 1869, he obtained his doctorate in philosophy from the University of Zürich, which was housed in the same building as the Polytechnic School and to which he had submitted his thesis on gases.

His biographer, Dr. Otto Glasser, describes him at this time

as tall and handsome with clear, penetrating eyes and dressed as the fashion of the day decreed: dark coat, gray trousers, soft collar with a large wing tie, and a gold watch chain around his neck.

Now a promising young physicist, Roentgen received an appointment as assistant to August Kundt, professor of physics at the Polytechnic School, and when Kundt was called to the University of Würzburg in 1870 he took his young colleague with him.

On January 19, 1872, Roentgen married Anna Bertha Ludwig, of Zürich, a tall, slender, well-educated girl of extraordinary charm and his senior by six years, whom he had known during his student days there. The newly married pair settled down in a modest house in Würzburg, but all did not go quite so merrily as the proverbial marriage bell. Spoiled by his parents and accustomed for a number of years to the freedom of independent living, the young husband was not easily domesticated. Adjustments were sometimes difficult, and on one occasion an argument in the street reached such a pitch that he hailed a passing cab and sent his wife home alone. To add to their difficulties they had but little money, and in the early days of their marriage Bertha had to do her own cooking, sewing, washing, and mending, a situation that did not tend to oil the domestic wheels. But they were young, and overcame their little temporary differences promptly and with good humor.

By nature the kindest of men, Roentgen may have been a little irritable at home because he was not entirely happy in his work. The laboratory was poorly equipped and, more important still, he found himself held back by an inadequate formal education. Before he could achieve a salaried position on the faculty he would have to be appointed a privatdocent, or unpaid lecturer recognized by the University, but as he lacked the requisite training in the classics he was prevented by the rigid tradition of this old institution from winning the coveted title.

The embarrassing situation was fortunately relieved in April, 1872, when he accompanied Kundt to the Kaiser-Wilhelms University in Strasbourg, which had been reopened after the Franco-

Prussian War and occupied handsome, well-appointed buildings. Here the Roentgens found a delightfully youthful and liberal atmosphere, entirely free from the stodgy tradition to which they had been accustomed, and after two years of hard work Roentgen was appointed a privatdocent.

Since he was now recognized as an able experimentalist and an earnest though not a brilliant lecturer he was offered three years later, and accepted, a full professorship in the Agricultural Academy at Hohenheim, a village in Württemberg. But the facilities there proved even less adequate than those in Würzburg, and he was unable to do any creditable work. Then, too, he and his wife missed their Strasbourg friends and, what was worse, vermin overran their apartment. He wrote in a letter, though, that they had established more or less friendly relations with the rats, which procured their daily food from the kitchen scraps and in return left him and his wife in relative peace; as for the cockroaches and bugs, she soon gained the mastery over them.[2]

It is no matter for surprise, therefore, that a year and a half later he gladly accepted an offer to return to Strasbourg as an associate professor of theoretical physics.[3] Here he continued his work on the physical properties of gases, and among other things undertook the investigation of certain electrical phenomena and of crystals. In the course of this work he showed himself to be an ideal experimental physicist, for he saw each problem clearly, tested his findings rigidly before publication, and described them briefly but precisely.

Hence it was but natural that in 1879 he should have been recommended by the leading physicists of Germany for the chair of physics at the University of Giessen. Finishing his work on crystals, he inaugurated a series of investigations on heat, designed and made delicate measuring instruments, and finally developed such skill in determining small physical effects that many of his findings remain unchallenged to this day. Here, too, he became financially independent for the first time, perhaps through the death of his father in 1884.

He was able to attack all these many and varied problems because of his unusual knowledge of the literature, which he often

sat reading until far into the night. Less industrious with his pen, he could force himself to describe his results for publication only after the greatest effort. His mind was active and inquiring, his interest quickly transferred to new problems, and often he became so absorbed in these as to lose interest in the description of finished work.

Over and over again he received gratifying recognition of his ability. In 1886 the University of Jena invited him to occupy its chair of physics, and two years later he was offered a similar position at the University of Utrecht. Both were declined, and as he was thoroughly human it must have given him peculiar satisfaction to refuse the latter invitation, from the university that had once rejected him as a regular student.

But on October 1, 1888, when he was forty-three years of age, there came an offer that could hardly be declined—the post of professor of physics and director of the new physical institute at the University of Würzburg. Situated on the broad, tree-lined Pleicher Ring, which was later to be called Roentgen Ring, the building had two spacious floors in addition to a basement, and a lecture room. The second floor contained the private living quarters of the director and much to the delight of Mrs. Roentgen, who had always been deeply interested in flowers, there was ample room for a conservatory.

The return to Würzburg was something of a triumph. They had arrived there sixteen years before as a young married couple, optimistic yet uncertain about the future, and soon to be bitterly disappointed when the University refused to give Roentgen the academic title upon which all his advance depended. Now, with his reputation firmly established, they were quickly taken up by the inner circle at the University and almost immediately were enjoying an active social life among a large group of friends.

Here the new professor worked chiefly on the physical properties of various liquids and solids, but that his interest was not wholly confined to experimental physics is shown by his election, in 1894, to the rectorship of the University, the highest office that it could bestow.

Now in his fiftieth year, Roentgen was one of the world's

leading physicists, and might well have rested content with the position that he had gained by his enormous and varied labors. But with the perennial interest of the scientist he was captivated by the new investigations on cathode "rays," and finally became so absorbed in repeating some of the experimental work that he decided to drop everything else in its favor.

Late in the afternoon of Friday, November 8, 1895, working alone in the laboratory as he preferred to do, Roentgen had carefully enclosed a modified Crookes tube in a black cardboard jacket to screen out all visible glow from it. Turning his eyes aside for a moment to make sure that there was none, he saw, in a phrase borrowed from Wordsworth by the celebrated English physicist, Silvanus P. Thompson, a light that never was, on sea or land: [5] a weak glow shimmering on a bench near by like faint green clouds, and moving in unison with the alternating electric discharges that he was passing through the tube.[3] He lighted a match, and discovered to his surprise that the source of this mysterious phenomenon was a small fluorescent cardboard screen that he had coated with barium platinocyanide for the detection of cathode "rays." He repeated the experiment again and again, moving the screen farther away from the tube each time, and continued to get the same result. Something that the eye alone could not perceive was emanating from the tube and making itself visible by its effect on the fluorescent screen!

He became absorbed in attempting to explain a phenomenon that contradicted everything known about cathode "rays," since these never penetrated more than an inch or so of air. His concentration was so intense that he grew oblivious to all else, and completely unaware of the passage of time. An assistant knocked at the door, entered the room in search of a piece of apparatus, and left without having been noticed. Still the hours flew by. Several times as the evening wore on Mrs. Roentgen dispatched a servant to call him to dinner, and when he finally sat down at the table he ate but little, and that little in almost complete silence. When his wife asked him what was wrong he made no reply, and she ascribed his silence and his abrupt return to the

laboratory in a state of suppressed excitement to a fit of ill-humor.

Profiting by the absence of students over the week end, he went back to his laboratory early on Saturday morning to repeat the experiment of the night before. Then, in weeks of feverish activity during which he ate and even slept there, he devoted himself exclusively to discovering what other properties this curious emanation might have.

If it could penetrate air it might be able to pass through other substances also. To test the truth of the conjecture he interposed various objects between the tube and the screen—a piece of paper, a double deck of playing cards, a thick book, wood, hard rubber, and sheets of different metals. The invisible something passed through them all with the exception of a thin sheet of lead, and caused the fluorescent screen to glow. To examine further the ability of lead to stop the emanation, which he had now begun to think of as rays, he selected a small piece of the metal and was amazed to find that he could distinguish the outlines of the thumb and finger holding it, and within this a darker shadow: the bones of his hand!

During the closing weeks of 1895 he worked in entire seclusion, first to convince himself that his chance observation represented a fact, and then to build up sufficient faith in his discovery to hand it over to other investigators for either confirmation or refutation. To a scientific friend who inquired impatiently what was going on, Roentgen said that he had discovered something interesting but was not yet sure that his observations were correct.

Knowing that cathode "rays" darken a photographic plate, he set out to determine whether the radiation from his Crookes tube would produce a similar effect. After finding that it did he persuaded Mrs. Roentgen one evening to be the subject of an experiment. She placed her hand on a loaded plateholder, he directed the rays from his tube on it for fifteen minutes, and when the plate was developed the bones of the hand appeared light within the darker shadow of the surrounding flesh; two rings had almost completely stopped the rays, and were clearly visible

as light areas. Mrs. Roentgen could hardly believe that this bony hand was hers, and shuddered at the thought that she was seeing her own skeleton; for to her, as to so many others later, the experience was uncanny and gave rise to a vague premonition of death.

Once convinced that his observations were trustworthy, the discoverer realized that early publication was essential. The last days of December were spent accordingly in assembling his notes, and a few days after Christmas he gave the secretary of the Würzburg Physical-Medical Society the manuscript of his paper: On a New Kind of Rays (A Preliminary Communication). In it he described his experiments, proved that the new rays were not cathode "rays," suggested some relationship to light, and proposed that they be called X rays in order to distinguish them from other rays and also because their nature was unknown.

On the night of January 23, 1896, Roentgen gave a public lecture in his institute. Every seat was filled long before the meeting opened and upon his entry he was greeted with a storm of applause, which broke out again and again as his talk progressed. When it was over Albrecht von Kölliker, the famous anatomist of the University, led the audience in cheers and said that the rays should be called Roentgen rays, an idea that was tumultuously approved by his listeners. Over a glass of beer later von Kölliker asked Roentgen whether it would be possible to make X-ray photographs of parts of the body that were larger than the hand, and whether medicine and surgery might not profit by the discovery. One obstacle seemed to be the almost equal density of the various organs, which, unlike the bones, could not be differentiated by the rays. Roentgen answered that it should soon be possible to employ them in medicine, and expressed himself willing to give the benefit of his experience to anyone undertaking such experiments in a medical institution.

Despite some openly expressed skepticism on the part of physicians and surgeons, the University of Würzburg conferred on Roentgen the honorary degree of Doctor of Medicine, on March 3, 1896.

Meanwhile pandemonium had broken loose. Almost over-

night he had become a focus of international praise and condemnation, for the daily papers everywhere were filled with the news and often embellished it with fantastic speculation. The medical journals soon followed, and from every quarter of the world came letters of congratulation. Through the doors of his institute passed scientists, reporters, and mere curiosity-seekers, some of whom did not hesitate to filch his X-ray photographs. Postal cards bearing Roentgen's signature mysteriously failed to reach their destinations. His mail was full of popular magazines with cartoons and stories of human interest. Letters arrived bearing advice on the best ways of exploiting the discovery for monetary gain. But how little their writers knew this great man, or were able to understand his belief that discoveries by German university professors belong to the world and should not be restricted by patents or controlled by any one group.

The location of their home in the institute left Roentgen and his wife no escape from the invasion. She complained to a friend that their domestic peace was gone, and he himself was annoyed and perplexed by the excitement and the confusion of voices. Yet the situation had its ludicrous side as well, which no doubt would have amused him, with his impish sense of humor, had he not been so distressed by the clamor.

Spiritualists maintained that his work proved as well as any material experiment could the existence of a spiritual body in accordance with the teaching of St. Paul, for which the natural body was but an envelope. Prohibitionists thought that the new rays would rapidly advance the temperance movement, by showing those who smoked and drank the progressive damage to their systems brought about by these deplorable habits. Grave fears were expressed, too, that woman's modesty would no longer be safe from assault, and a London firm was quick to respond with an advertisement of underclothing that was impenetrable by X rays, while across the sea a bill was introduced into the New Jersey State Legislature prohibiting the use of X rays in opera glasses. But let us not be too hard on New Jersey. A New York newspaper said that the new rays were being employed in a large medical school in that city to reflect anatomical diagrams directly

into the brains of its students, where they made a more lasting impression than did the ordinary method of learning the details of anatomy.

The tumult and the shouting did not die, and at last it became too much for the Roentgens. They fled. Almost as fugitives they left Würzburg on March 10, 1896, to seek quiet in Italy, but soon found that fame had traveled before them. Roentgen was recognized in the railway station at Munich and had to decline an invitation to lecture, while in Rome a newspaper reported his presence and he had to refuse two invitations. Until the travelers reached Sorrento he had hardly a moment to himself.

Leaving there at the end of March they went on to Lake Como. Here, at a dinner given to celebrate Roentgen's fifty-first birthday, an old friend enthusiastically repeated von Kölliker's proposal that the new rays be named after their discoverer. Although greatly pleased by this tribute from such a source, Roentgen objected strongly to the association of any person's name with a natural phenomenon, a stand to which he consistently held for the remainder of his life. He not only insisted on the term "X rays," but deeply resented the use of his name in connection with them.

After having visited Zürich and Baden-Baden the travelers returned to Würzburg early in the summer of 1896, only to meet still another annoyance. Now it was being asserted in some quarters that Roentgen was not really the discoverer of the X rays. The attacks, which were usually foolish and sometimes actually vicious, continued even after his death to belittle his accomplishment by ascribing the discovery to an assistant or a laboratory helper. Others, again, said that the discovery was wholly accidental. Now the presence of the fluorescent screen on a laboratory table at the exact point where it would encounter the emanation from his tube was a product of chance, certainly, but Roentgen knew the physics of his day in all its branches. Here was something entirely new that demanded explanation, so instead of simply marveling at the pretty glow and then passing on to something else, he began to investigate it. Opportunity knocks on many doors, but only the trained mind hears its call.

During the summer of 1896 he was flooded with invitations to lecture, and he and his wife had to flee once more. In Switzerland, where they were objects of public curiosity, they were forced to keep moving from place to place in order to escape the crowds until at last they took refuge in the home of old friends at Pontresina. Here the young grandson of the house noticed a great change in Roentgen. He who had been in the habit of taking a camera with him everywhere, for his favorite hobby was photography, was now camera-shy!

Offers continued to pour in from one university after another, but all were refused. Finally, however, at the special request of the Bavarian Government he agreed on April 1, 1900, to take over the new physical institute at the Ludwig-Maximilians University in Munich. Only with reluctance, though, for the living and working conditions in Würzburg had been highly satisfactory; moreover, the administrative work required by the new position would seriously limit the time available for research. Some members of the court circle in Munich received him and his wife coldly because of his earlier refusal to accept the privileges of nobility, including the prefix "von." But the attractions of art, science, and music exerted all their spell, and although he received many enticing offers he never could be persuaded to leave. Soon after having settled in Munich he leased hunting ground at Weilheim, and in 1904 bought a little cottage near by to remodel into a lodge. Curiously enough Roentgen was an excellent shot, even though it was difficult for him to distinguish red deer against their green background on account of color blindness, and vision in one eye had been considerably impaired by an illness in childhood.

Here in his little hunting lodge he was a jovial and charming host, entertaining his friends with amusing anecdotes and playing innocent pranks on them. He had a collection of pseudoscientific instruments, which it gave him the greatest pleasure to demonstrate. Among these there was one called "simplified X rays"—a little oblong box holding four wooden blocks that were numbered from 1 to 4. While Roentgen was out of the room his guests would arrange them in any desired sequence. Then, when he

returned, he would hold over the closed box an empty shell and, peering into it, correctly name the order in which the blocks had been placed. It was an ingenious trick. The shell exhibited to the guests was empty, and Roentgen would slyly replace it with a similar one containing a small compass. Tiny magnets were fastened to the blocks: to the upper end of number 1, the lower end of 2, and to the right and left sides of blocks 3 and 4 respectively. The compass in the shell pointed North for the first block, South for the second, and East or West for the two remaining, and thus each block could be located without fail.

His distinguished features, his penetrating gaze, his modest and unassuming manner marked Roentgen out as a man of extraordinary character. Indeed, he was described by the daughter of an intimate friend as a personification of the nineteenth-century ideal: robust, erect, vigorous, and devoted to his science; full of humor, never arrogant or biased, but open to everything new that did not seem to him extravagant or just superficially clever.[2] Yet notwithstanding his inherently lovable and courteous nature a certain shyness, amounting almost to diffidence, took possession of him in the presence of strangers and with the passage of time built a guardian wall that protected him from the advances of the self-seeking or merely curious.[3] At the same time it served to discourage many a more sincere caller; but once sure that a person was genuine Roentgen lost all his reserve, and with those fortunate enough to be admitted to close friendship he kept faith until the end.

One amiable little weakness was a liking for strong Dutch tobacco, smoked preferably in clay pipes. These really tasted best, he insisted, a proof that not everything had to be expensive in order to be good.

He was the recipient of almost countless honors, and seldom have such distinctions been more thoroughly deserved: a bronze statue in Berlin; one similar in Munich and, after his death, another in Leningrad; the Rumford Medal of the Royal Society of London; the Elliot-Cresson Medal of the Franklin Institute, in Philadelphia; the Barnard Medal from Columbia University, in

New York; and many others. In 1901, the year of its foundation, the Nobel Prize in Physics was awarded him, and contrary to his usual rule of not attending the bestowal of an honor he traveled to Stockholm to receive it. Characteristically, he gave the prize money to the University of Würzburg, to be used in the interest of science.

The outbreak of World War I and the final defeat of Germany affected this great man deeply, in particular because science felt the impact of prejudices aroused by the conflict. Besides bearing the burden of increased responsibilities in teaching and research incident to the war, he was depressed by his wife's illness. The pain caused by an inoperable stone in the kidney required that he give her as many as five injections of morphine every day, and during the war years he could never leave her for more than a few hours at a time. She died in an attack on October 31, 1919, at the age of eighty.

The memory of well-nigh fifty years of loving companionship increased Roentgen's sense of loss, and in his loneliness he used to read important news items to her picture, pretending that she was still with him to share his thoughts. In general his own health had been good, although he had had a rather serious operation on one of his ears, from which he quickly recovered.

He was greatly consoled throughout the trying years of war by the thought that his discovery had contributed so much to the amelioration of pain and the saving of soldiers' lives, but on the other hand much distressed by a wholly different result of his rays. From laboratories all over the world had been coming accounts of a reaction in the skin after exposure that resembled sunburn at first but was soon followed by intensely painful ulcerations and only too often by cancer, which caused the loss not only of limbs but of lives. Roentgen himself did not suffer because he had been protected from the first without knowing it. He had carried out his experiments in a large zinc box that shielded his instruments against static electricity emanating from the Crookes tube, the conducting wires, and so on. In this box he remained with his measuring apparatus, the rays entering through a win-

dow cut in its walls. For reasons of his own he had added a lead plate to the zinc wall between the tube and his body, and so had worked in safety.

Roentgen was now a desolate old man, for he had survived not only his wife but many friends also. Futhermore, he had lost a very comfortable fortune by changing his foreign investments into German war loan bonds. One of the few pleasures left him was a lively correspondence with those friends who still remained, in which he liked to recall vacation days of the past. In his closing years a lifelong love for the Swiss mountains had been intensified, but professional responsibilities and his wife's last illness had kept him at home, while after the war the journey was made impossible by inflation of the German mark.

In 1921 he was urged to spend the summer in Switzerland as the guest of a friend, and so was enabled to see the Engadine once more. In the following year he visited his friend a second time, and on August 9, 1922, made the last trip into his beloved mountains. Upon returning to the laboratory he resumed his work with a new enthusiasm, for the holiday had renewed his energy, and although he was easily fatigued and his vision no longer keen enough for accurate observations he kept on until a few days before his death.

The gastrointestinal distress from which he had suffered for the past year now returned. He diagnosed his illness as cancer of the intestine, but the director of the medical clinic at the University did not agree, and assured him that there was no cause for alarm. This may have been merely to comfort him in the face of an inoperable growth; in any case, he died of the disease that he himself had identified, on the morning of February 10, 1923, at the age of seventy-eight. His ashes lie beside those of his wife in the cemetery at Giessen.

Hardly had the X rays been discovered before the apparatus for eliciting them began to undergo improvement, as a result of Roentgen's refusal to hamper the development of his finding in any way. He had shown that the rays emanated from the glass wall of his Crookes tube, at the point where the electron stream,

or cathode "ray," impinged on it, but before long it was found that a bit of platinum, mounted in the center of the tube, made a more efficient target, to employ the modern term.[7] In a tube widely used nowadays the target is made of tungsten, but no matter what material arrests the electrons in their flight, X rays emerge as a result of the sudden change in their velocity.

Much of the work of Roentgen's colleagues was directed toward identifying the nature of these rays, and in 1912 they were shown to be of the same character as light, though because of their extremely short wave length they cannot be seen.[3]

Fifty years after the great discovery constant improvements in the manufacture of glass, in the evacuation of tubes, and in other technical procedures had brought forth a series of tubes running from that used in dentistry, and about the size of a finger, up to a nine-foot giant the rays from which can penetrate twelve inches of steel. Roentgen's induction coil, which provided electrical discharges that alternated back and forth at an intensity of about 10,000 volts,[8] had been replaced by transformers delivering impulses that move in the same direction and may have a potential as high as several million volts. With improvements in apparatus and in the photographic films employed, the exposure for an X-ray photograph has been reduced from the twenty minutes necessary in 1896 to as little as a fraction of a second for tissues that are easily penetrated by the rays.

Only for a short time was the use of the X ray in medicine and surgery limited to the diagnosis of fractures and the localization of foreign bodies such as bullets. The rays were soon employed in seeking out concretions like gallstones, and it was realized almost immediately that hollow organs not ordinarily visible in roentgenograms might be seen if they were filled with something that the rays cannot pass through. Some of the earliest photographs taken in Vienna about 1896 showed the veins of an animal in beautiful relief after they had been injected with a mixture of lime, mercuric sulphide, and petroleum, but obviously this method could not be used in the human subject.[3] The real advance was made by the distinguished American physiologist, Walter B. Cannon, while he was still a medical student. In De-

cember, 1896, he began feeding bismuth subnitrate to small laboratory animals and following the course of this material with a fluorescent screen; for any opaque object between the rays and the screen throws a sharp shadow on its brilliantly glowing surface.

In 1904 the procedure was extended by others to the human patient, but the less dangerous barium sulphate was substituted for the bismuth salt. The subject having drunk a glass of an appropriate mixture, this opaque material is photographed as it passes down the gastrointestinal canal, and examination of the pictures enables the physician to diagnose many diseases of the digestive tract and to follow the results of his treatment. In a similar way the other organs can be studied after the ingestion or injection of suitable agents.[6, 7]

Diagnosis is perhaps the most important function of the X rays in medicine and surgery. Their use in treatment is severely limited by the fact that although they destroy diseased tissues they destroy healthy ones also, and the margin between an effective and a dangerous dose is narrow indeed. Nevertheless they will cure a few types of malignant tumors without damage to the surrounding structures, and progress is constantly being made. Even though they do not cure they may delay the growth of a cancer and so afford the patient months of relative comfort—but now we are trespassing on the province of the specialist.

XIII

HEREDITY

IN the little Moravian village of Heinzendorf, an island of German-speaking folk entirely surrounded by Czechs, a son was born in 1822 to Anton Mendel and his wife Rosina, nee Schwirtlich, and christened Johann.[2] The exact date of this significant event is unknown: July 20 according to some, July 22 according to other sources. Many of the characteristics that appeared as the boy grew older, the gentle face, the high forehead, the intellectual capacity, were contributed by the mother, who is described by Iltis, Mendel's biographer, as even-tempered, quiet, and unassuming. From the father's side came the small stature and the aptitude for gardening.

When Anton Mendel was not laboring in the fields he spent the time grafting fruit trees in his orchard, and often took the child with him. Thus a love of nature was awakened in the boy and to the last years of his life, long after he had given up botany, he retained his interest in fruit culture, as the superior products that he raised for his monastery bore ample witness.

In early youth Johann was short, broad-shouldered, sturdy, and skillful in agricultural work to the great joy of his father, whose dearest wish it was that the lad grow up to be an able husbandman to whom the farm could be safely bequeathed. But the mother had dreams, as mothers will, of seeing her son develop into something more than a mere farmer, for the village schoolmaster had taken note of the boy's exceptional ability and had not failed to bring it to the attention of his parents. Furthermore, two older companions had entered a more advanced school in Leipnik, about ten miles distant, and during vacations the little lad was entertained with accounts of their marvelous adventures. Johann pleaded with his father to be sent there too, and when the mother added her entreaties Anton Mendel saw his cherished

plan gravely threatened; yet could not close his eyes to the fact that only through education could his son escape the hard lot of a peasant.

In the end the eleven-year-old boy had his way, was enrolled provisionally in the school, and before long stood at the head of his class. With thankful hearts his parents entered him in a still higher school at Troppau toward the close of the year 1834. But in their straitened circumstances they found it difficult as time went on to continue their child's education, and since they could send him only bread and butter from home he had to shift for himself as best he might. It was a trying experience for the lad, who often sat hungry over his books and whose studious habits allowed no time for rest; even the summer holidays brought no proper relaxation, since help was needed on his father's farm. The natural result was a grave illness that sent Johann home in the spring of 1839 and kept him there until the following September. Yet in spite of all obstacles he made an enviable record and upon graduating in August, 1840, received a testimonial to his diligence and his brilliant gifts.

In the following year he went to Olmütz to continue his studies, where twice more he was laid low by protracted and threatening illness, the nature of which, like that of the first, cannot be determined after all these years. Hardships and poverty further threatened his future, but at the critical moment his younger sister came to the rescue by renouncing a part of the inheritance that their parents had set aside for her. He never forgot this generous act, and in after years amply reimbursed her three sons.

At the end of his course he felt it necessary to seek some station in life where he would be liberated from bitter need, and requested help and advice from one of his teachers. It so happened that this professor, who was well acquainted with many of the brothers in the Königinkloster at Brünn, had just been asked to suggest suitable candidates for their monastery, and proposed Mendel's name.

Before admission, early in September, 1843, the applicant was given a physical examination and found to be in perfect health, so that his illnesses, serious though they seemed at the time, ap-

pear to have left no mark. Having obtained his bishop's consent during the interim, Mendel donned the robe of a novice on October 9 and, after the custom of his Church, took another name, Gregor, which ever afterward preceded his given name.

"By this step," Mendel wrote in his autobiography,

> his material position underwent a complete change. Amidst physical comforts so advantageous for study courage and strength returned . . . and he attacked the classical subjects prescribed for his year of probation with the greatest delight. During his free hours he busied himself in the little botanical and mineralogical collection that was at his disposal in the monastery, his interest in natural history increasing daily as he found opportunity to become familiar with it. . . . the study of nature became so entrancing that he shrank from no exertion to fill the gaps still present by self-instruction and the advice of men with practical experience.

In 1845 Mendel entered upon a four-year course in theology at a seminary in Brünn and proved to be, as he always had, an industrious and gifted student. But because death in the meantime had claimed so many of his monastery brothers that it was becoming difficult to carry on the work of the order, and because of his excellent record, he was ordained a priest after having completed only three years of study.

He seems to have taken little pleasure in his curacy. The population of Brünn was predominantly German, but as there was a considerable admixture of Czechs he had to familiarize himself with a language that was strange to him and, what was worse, preach in it as occasion required. Then, too, the sight of illness, suffering, and death unnerved him. Involuntarily he shrank from it, and at last became so dangerously ill that his prelate requested the bishop to relieve the young priest of his clerical duties. Once again the nature of his illness remains undetermined, but his biographer suggests that it may have been a morbid depression leading in the end to a severe nervous disorder of some kind.

Now twenty-seven years of age, Mendel was appointed a substitute teacher of elementary mathematics and Greek in the high-school at Znaim, and gladly did he welcome this change of scene

and occupation. Naturally enough, for his future career shows that he was far better suited to teaching and research than to the care of souls.

Znaim was beautifully situated on a winding river not far from the German-Austrian frontier, and many inhabitants of the district were engaged in viniculture. Their sedulous wine bibbing did little to encourage mental alertness, though numbered among them were a writer of some note and a clergyman of scientific attainments. The latter, Prokop Diwisch by name, contrived and installed independently in 1754 a lightning rod that in the manner of its connection to earth was superior to Benjamin Franklin's, invented but a few years before. The scientific world, however, paid not the slightest attention to it.

Although Mendel was accounted a "good citizen" he was by no means a lamb for gentleness, as the following anecdote goes to prove. One day while his school was being inspected by the Bishop of Brünn, who was enormously stout, the young teacher was indiscreet enough to say: "That man is more burdened by fat than by brains." The remark came at once to the ears of the Bishop, of course, and from that day forward Mendel was in the great man's black books. In later years he was punished by fate for this bit of malice since he, too, developed an imposing façade.

In reality he was kindhearted, and the idol of all his colleagues and students. Hence the principal of the school would have been glad to keep him on permanently, but this would have required that he pass a government examination for which candidates generally prepared themselves by several years of university training. Though he lacked this essential his principal and his fellow teachers encouraged the attempt, which was doomed to failure from the first and never would have been made by such a cautious man as Mendel had it not been for their ill-advised optimism.

After his unsuccessful endeavor he returned to Brünn, in the summer of 1850, richer by a grievous disappointment. The examiners had reported that the candidate lacked neither talent

nor industry, but obviously had not enjoyed the benefits of a formal higher education. Impressed by his manner nevertheless, one of them was instrumental in procuring his admission to the University of Vienna, all expenses to be paid by his monastery, in order that the deficiency might be repaired. The bishop agreed on condition that the young monk live like a monk during his sojourn in the gay capital, so it was arranged that he was to lodge at a monastery of hospitallers. In a letter to its prior Mendel's prelate stipulated that lest otherwise the student be diverted from his sacred calling he was to be given a small room, a midday meal, and a light supper but no beer and no wine.

During his four semesters at the University, from 1851 to 1853, he took courses in physics, chemistry, zoology, botany, mathematics, and paleontology, besides attending private lectures on entomology. On his certificate of domicile, which had to be shown to the police at each arrival and departure of the bearer, he was described in the following words. "Stature: Medium. Hair: Light. Eyes: Gray. Distinguishing characteristics: None. Speaks: German." No distinguishing characteristics! But had the police been able to look into that mind and that heart, they would have found them in full measure.

Now, at the age of thirty-one, Mendel was at last equipped, and in the spring of 1854 he began to teach physics and natural history in a government secondary school at Brünn, where he remained for fourteen years. This period, which included his active research, was the happiest of his life. Not only did he find quiet pleasure among his bees and his flowers; he possessed in addition the proud knowledge of having entered into a previously unknown land. The gift of lucid exposition that marked him as an investigator distinguished him also as a teacher and made him unexcelled in this exacting profession, yet he remained simple and unaffected, a just and kindly friend to all his pupils.

"I can still see him," said one in after years, ". . . a man of medium height, broad-shouldered and rather stout, with large head, high forehead, and gold-rimmed spectacles before pleasant yet penetrating blue [*sic*] eyes. Almost always he wore the same

costume, the secular garb for a priest of his order; a silk hat . . . a long, black frock coat that was generally too large, and short trousers tucked into high, tight boots."

Others spoke of his patient and inspiring manner in the classroom, his noble character, his gentle face, his winning smile, his clear and pleasant voice. He was a popular, yes, even a beloved teacher, who almost never "flunked" one of his charges. Fond of birds and animals, he abhorred snakes and would have nothing to do with them. Former students told his biographer of a pet fox that was allowed to run free in the monastery garden at night and was tied up each morning, as well as of a tame hedgehog that crept into his boot while he slept and gave rise to an unpleasant encounter when he arose the next day and tried to dress.

It has been said that Mendel had a colony of mice in one of his two rooms at the monastery, and that he crossed white and gray ones. Perhaps he did, and it may very well be that his first ideas on inheritance arose from such experiments, but in any case he never mentioned them. This is not surprising, however, since a priest who occupied himself with science of any sort would already have been suspect in the eyes of ecclesiastical zealots, and to watch the mating of animals would have been thought downright immoral. Furthermore, he had to be especially careful because his bishop was not well-disposed toward him, for a reason already given. Thus he may have turned from shocking experiments with mice to the less questionable study of flowers.

Behind the main monastery building, where the windows of the library looked out upon the garden, lay a small plot hardly exceeding 20 × 100 feet in size. But it is historic ground. There, on calm spring days, Mendel bent over his garden peas, opening the immature blossoms and removing their stamens before any pollen had been shed in order to prevent self-pollination, then brushing upon the stigmas some pollen from another plant that he had selected as the opposite parent in a cross. Finally, to guard against the deposition of unwelcome pollen by wind or insects with consequent vitiation of the experiments, he covered each treated flower with a tulle or paper cap.

MENDEL'S GARDEN

Such a careful investigator was this little priest that his experiments in the open air were checked by others conducted in a greenhouse, as an extra precaution against unwanted pollen. Indeed, no amount of labor could exhaust his patience. "The experiments go on but slowly. At first they required a great deal of patience," he wrote to a friend, "but later, when several were in progress at once, the affair went better. Then interest was intensified daily from spring until fall, and the pains that had been taken with my charges found abundant reward. If incidentally I should succeed in advancing the solution of the problem in any way by my experiments I shall be doubly happy." [2]

Industrious experimentalists had been piling fact on fact for decades, and accumulating an enormous amount of detailed information that no one knew how to analyze. They had summarized in their minds the entire make-up of the parent plants and then sought to find similar types again among the descendants, but the endlessly complicated profusion of characters made it impossible to go further than to establish the observation that hybrids resemble one or the other parent or are intermediate between them. Mendel, on the contrary, was satisfied to choose plants that differed in but one or a few constant and definite characters and to follow only these in the progeny, closing his eyes to all others. Thus when he bred a garden pea with white flowers to one with red, say, he paid attention in his first experiments to blossom color alone and disregarded entirely such other characters as height of stem and appearance of seed. Not until later, when the behavior of single traits had been established, did he venture to extend his analysis by studying two at a time. Attacking the problem little by little in this way he succeeded, where others had failed, in bringing order out of chaos. Here the lines of Alexander Pope may fittingly be applied, with an appropriate change of name:

> Nature and Nature's laws lay hid in night:
> God said, *Let Newton be!* and all was light.

But this was not the only advance initiated by Mendel's genius. He gathered and sowed the seed separately, kept precise

records of the number of each type of progeny, assembled them in separate classes, and calculated the relative size of these groups. In so doing he became the first investigator to introduce quantitative methods into the study of heredity, and raised genetics to the dignity of a science. Well aware of the difficulties that lay in his path, he wrote in a letter:

> No one who realizes the scope of the problem and can measure the obstacles that experiments of this sort have to surmount will be surprised that a general law for the constitution and evolution of hybrids has not yet been established. Final decision cannot be achieved until detailed experiments on the most varied families of plants are available. Whoever reviews the work in this field will be convinced that among the many attempts not one has been carried out in a way and to an extent that would make it possible to determine the number of various forms under which the descendants of hybrids appear, and to arrange these forms with assurance in the single generations and establish their numerical relationships. The undertaking of such an extensive investigation requires some courage, to be sure; yet it appears to be the only way in which a problem can finally be solved whose significance in the developmental history of organic forms cannot be overestimated.[2]

From 34 different kinds of garden peas that had been tested by two years' breeding to make sure that each was of pure strain, he finally chose 22 for his experiments. Seven pairs of contrasting characteristics were selected for examination, and in each of his seven experiments 287 crosses were made on 70 plants. "The true relationship," he wrote, "can be represented only by the average of as many single values as possible; the greater the number of these, the more certainly will pure chance be eliminated."

Two years spent in merely preparing for an experiment, yet the impulsive Metchnikoff found it hard to wait overnight for the outcome of his!

How Mendel loved to linger among his flowers is shown by the pleasantry with which he used to amuse visitors. "Wait," he would say, "now I will show you my children." Then he would

lead the strangers, confounded at such a frank declaration from a priest, to the peas in his little garden.

One of the first facts with which they rewarded his care was this: that the two members of a pair of contrasting characters differ greatly in their ability to express themselves in the hybrids of an F_1, a first filial generation, as it is now called. The offspring of a white-flowered and a red-flowered plant, for example, all bore red blossoms; hence Mendel referred to this color as dominant, and to white as recessive. Whiteness had not disappeared, however, for it emerged again in the F_2 and following generations.

Though complete dominance like this of one character over another is often seen it is not the invariable rule, as later work by Mendel and others soon showed.[9] Thus red snapdragons crossed with white ones produce an F_1 generation with pink flowers; dominance is incomplete, neither red nor white prevailing, and the blossoms are intermediate in color between those of the two parent plants. Both red and white are separately present, however, for an F_2 generation contains red, pink, and white flowers.

The behavior of two unit characters like red and white in garden peas led Mendel to his great discovery: the independence, or segregation, of all inherited traits. But neither he nor his successors could distinguish sharply in their day between these visible characters and the influence that resides in the sex cells and causes each trait to develop. This has been identified since then and called a gene. Almost inconceivably minute, the genes are pictured as strung out like beads along the network of the cell nucleus and it is they that are inherited, not the characters over which they preside. When the sex cells, or gametes, unite the offspring receive genes for the characters of the male and the female parent, and these pass independently and intact through all the succeeding generations. They never fuse.

For a time the brown color of the mulatto was regarded as a contradiction of Mendel's findings and ascribed to "blending in-

heritance," because genes for black and white were supposed to combine.[8] But if they did the children of mulattoes would all be brown like the parents, whereas they run from the deepest black to nearly white. So it is assumed that Negroes have genes for different shades of black and brown, and whites for various tints of white. Some of each are contributed by the parents, but remain as separate as the genes of a snapdragon. The blending is only apparent.

This disposes of all those sensational tales in which a woman who seems to be white though she has some hidden Negro blood, and is married to a white man, gives birth to a coal-black baby. Such a remarkable occurrence would be possible only if both parents had some hidden Negro blood, or if the paternity of the child were in doubt.

It grew clear as time passed that Mendel's findings, fundamental though they were, could not of themselves explain all the facts of heredity. It is now realized that the same gene may elicit a variety of effects on many characters, since it operates against the entire genetic and environmental background of an individual rather than independently of all other genes.[6]

Mendel had always been cramped for space in his little garden though after 1868, when he became abbot of the monastery, room was available for experiments on other plants. But time, also, had been meted out with a sparing hand, and he expressed the deepest regret that he could not undertake many field trips for the purpose of gathering wild specimens.

"My strenuous duties at the school often prevent me from getting out into the open, and by vacation time it is too late for many things. . . ." But the blame had to be shared. ". . . I am no longer exactly suited to botanical excursions for Heaven has blessed me with overweight, which becomes very noticeable on long walks and especially in climbing hills, as a result of universal gravitation."[2]

The hope that he might enjoy some leisure after having become familiar with the work of his new office was never quite fulfilled, and the experiments on hybridization were discon-

tinued after 1871. New duties and new burdens arrived with every passing day, among them a long, wearisome, and defiant struggle with the government over taxation of the monasteries. Yet all this alone would not have sufficed to take him from the experimental work so auspiciously begun, for he was still able to devote some time to his bees and his meteorological observations. The truth is that he was discouraged because there was no one to understand him, no one that might have believed in him; his enormous labors had awakened no echo. Furthermore, the profound riddle of heredity to which his peas had given such a clear answer, though none of his contemporaries could grasp it, became ever more complex through his other experiments and especially those on hawkweed, which proved to be a thoroughly exasperating plant. Certainly this unassuming man was not primarily interested in renown, but such a lonely and discouraging struggle would paralyze any human power.

His revolutionary paper, read on a clear, cold February evening in 1865 before some forty members of the Naturforschender Verein, a society of experimental naturalists in Brünn, was not understood. Attention flagged when he described his method of calculating the ratios between various types of plants, and no doubt some of his audience were repelled by this marriage of mathematics and botany. Moreover, the scientific world was then in a turmoil over Darwin's *Origin of Species*, published only six years before, and the introduction of still another idea into biology seemed almost too much. The editor of the society's transactions, where the paper appeared in the following January, wrote with a pencil in the upper left-hand corner of the manuscript: "40 reprints." Forty, where nowadays they are ordered by the hundred, and with far less reason!

The article lay neglected for almost thirty-five years, since the transactions were not widely circulated at the time. Under a new policy, however, they were sent as an exchange in 1900 to more than 120 universities and scientific societies at home and abroad, and in that eventful year Mendel's contribution was independently discovered by three botanists, themselves students of heredity, in Germany, in Austria, and in Holland.

Immortality had come to the industrious little priest, but too late. His last illness, chronic Bright's disease, assumed a grave form in the autumn of 1883 and he was confined to his bed with generalized edema. On the morning of January 4 next he was able to dictate the results of some observations in meteorology, the science to which he had longest remained faithful, but almost immediately afterward his condition became so threatening that his physicians abandoned all hope, and he died in the early morning of Sunday, January 6, 1884.

With the discovery of Mendel's paper and the verification of his results on every hand, genetics began to make rapid strides. Among the significant investigations that followed were those of the Danish botanist, W. L. Johannsen, who bred what he called pure lines of beans, since they showed no hereditary variations whatsoever.[9] Enormous advances in plant and animal breeding were made and, what is of more interest to medicine, the establishment of inbred animal strains for experimental purposes was begun not many years later. Here the mouse proved especially useful because many tame varieties were already available; its small size makes it inexpensive to buy, house, and feed as well as easy to handle; and finally, large numbers of young are produced in rapid succession and mature quickly. Four or five generations can be raised in a single twelvemonth as contrasted with man, in whom the interval between generations is something like twenty-five years.

The mouse is peculiarly adapted to cancer research because cancer of the mammary gland, with all the features of this disease in woman, is very common in the females after they have reached middle age. It never appears spontaneously in the males but only, of course, because in them the gland is virtually nonexistent.

By mating the descendants of affected mice brother to sister and introducing no foreign element, as Johannsen raised his beans, inbred lines are obtained after about twenty generations in which the incidence of mammary cancer among the females may be as high as 90 per cent; similarly, breeding together the

descendants of female mice that are free of cancer will result in strains with an incidence of less than 1 per cent. It is to be clearly understood, however, that the disease itself is not inherited, but only the tendency to develop it in later life.

During the course of such experiments it was noticed that in respect to cancer incidence daughters resemble the mother more closely than they do the father. Thus females from a high-cancer strain crossed with males from a low one gave birth to progeny in which a large proportion of the females developed cancer. On the other hand, when females from a low-cancer strain were bred to males from a high strain the incidence among their offspring was almost nil.[4]

Obviously the mother exerts a commanding influence on the percentage of mammary cancer among her daughters. But how? The answer was supplied by the geneticist C. C. Little and his staff at the Jackson Memorial Laboratory, in Bar Harbor, Maine, whose work culminated in 1936 with the report by J. J. Bittner, a member of the group, that the milk is to blame. It was a real catastrophe when their laboratory, with its irreplaceable records and mouse strains, was destroyed by fire in the autumn of 1947.

When newborn mice were transferred from their own mothers to foster mothers it was found that less than 5 per cent of the females from a high-cancer strain that had been put to suck on mothers from a very low one ultimately developed mammary cancer, though 90 per cent would have done so had they been left to nurse on their own mothers. Conversely, among newborn females from a low-cancer strain put out to nurse on mothers from a high one, about 75 per cent finally developed cancer as a result. But this almost incredible fact proved to be true only for cancer of the mamma, experiments with many other kinds of malignant tumor having shown no such effect on the part of the milk.

It is not the milk itself that exerts the baneful influence, however; it is something in the milk that is almost certainly a virus, and continued investigation proved that it is unable to produce its effect alone. It requires the cooperation of at least two other

factors: a hereditary susceptibility of a nature so far unrecognized, and adequate hormonal stimulation of the mammary tissue, to which a third may perhaps be added; some sort of influence exerted by the mother upon the offspring while they are still in the uterus. Thus the initiation of mammary cancer in the mouse has turned out to be a far more complicated process than was at first suspected.

Cancer in other organs of the mouse, the liver and the bones among them, as well as leukemia, which may be described as cancer of the blood, has also been shown to arise on a hereditary basis.

These investigations on the genetics of mouse cancer suggest that anyone with a history of several cases of cancer in the family should be especially watchful, and seek trained advice at the slightest suspicion of trouble, for it would be dangerous to make a molehill out of a mountain. More cannot be said at present. Occurring rather late in life as it usually does, the disease offers a difficult problem. Suppose that a woman who would have died of cancer of the uterus if she had lived to the age of forty-five is killed in an automobile accident at the age of thirty, and her daughter is found years afterward to have cancer of the same organ. Who can tell whether or not a tendency was inherited from her mother? Yet despite the uncertainty that so often rules when observation must take the place of experiment, there are indications that cancer of the breast, uterus, prostate, stomach, and intestine, to mention only the common types, attack certain families more frequently than can be accounted for by mere chance.[7]

It is impossible to say at present whether human milk plays a role in eliciting cancer of the breast. Many years of careful observation and accurate recording will be necessary before this problem can be solved as it has been for the inbred mouse, the span of life being so much longer in man and inbreeding wholly out of the question. In the words of Johannsen: "From the point of view of a pure-bred dog, we are all curs."[3]

Whether or not cancer will finally be proved hereditary, there are certain abnormalities in which inheritance is definitely in-

volved, and certain diseases in which the evidence in favor of it is strong. Hemophilia, a dangerous predisposition to bleed profusely from the merest scratch, is well known to be passed from mothers to their sons, and is famous because it has afflicted European royalty: among them a son of Alfonso XIII of Spain, the Count of Covadonga, and the last Russian Czarevitch, both of whose mothers were granddaughters of Queen Victoria.[8]

Less serious defects also, like color blindness; deformities of the teeth; extra fingers or toes; the large protruding lower lip that can be traced through eighteen generations of Hapsburgs; and countless others are handed down from parents to their children.

As for actual diseases or, more accurately, a tendency to develop them, the rheumatism of childhood is thought by many to possess a hereditary background, and the same is true of tuberculosis. Given such factors as malnutrition and an unfavorable climate these diseases are very apt to make their appearance. Diabetes is in the same group, an inherited weakness making the bearer vulnerable; if he should overeat, or fret and worry to excess, sugar will not be properly used by the body and will appear in the blood and the urine. In the case of high blood pressure, arteriosclerosis or hardening of the arteries, and allergic diseases like hay fever and sensitivity to foods and other substances such as pollen, the evidence is less conclusive.[8] It will be complete some day, no doubt, considering the advances already made under severe handicaps, but before a defect or a weakness can be unhesitatingly referred to heredity it must undergo the most searching analysis by trained geneticists. The chance of error is great because the art of diagnosis has not yet reached perfection, the father's identity is not always certain, and the family history too often a matter of simple hearsay; but chiefly because the population, unlike that of a geneticist's animal colony, is not homogeneous and not maintained under uniformly similar conditions.

Human matings are never made in deference to the wishes of the geneticist but, from his standpoint, haphazardly, and the problem is complicated still further by the fact that many traits are influenced by environment. Yet despite all these difficulties

sufficient knowledge of human heredity has already been accumulated to permit some practical applications. Among them are the furnishing of advice in regard to prospective marriages, the determination of nonpaternity by examination of the blood, and in some small degree the recommendation of programs for the protection and improvement of society. So important have these applications become, indeed, that a new science of medical genetics is rapidly developing.

An excellent example of the first is provided by L. H. Snyder in *Genetics, Medicine, and Man,* from whose chapter on human heredity the material in this paragraph and the four following has been taken. A young married pair who had lost a first child from amaurotic familial idiocy, in which blindness, paralysis, and death occur in early infancy or childhood, asked whether they should have other children. Since the disease is now well understood in its genetic aspects it was possible to tell them that the chance of another child developing it was one in four.

As for the blood, the only reliable hereditary traits so far known are its agglutinogens. These stimulate the production of agglutinins, substances that cause the red cells to clump, and at least thirteen are known at present. By suitably combining them more than 2,500 types of blood can be accurately classified, and the blood of a child thus compared with that of a supposed father.

The most popular agglutinogen in the public eye is the Rh factor, so called because it was first discovered in the blood of rhesus monkeys. A first transfusion of blood containing it into an Rh negative person—one, that is, who has none of his own—causes no apparent trouble. Nevertheless, the recipient has formed protective substances, antibodies, against the Rh factor as against bacteria or any other foreign protein, and if later he should receive a second transfusion from an Rh positive donor the antibody content of his blood may rise high enough to agglutinate his red cells, perhaps with a fatal outcome.

Somewhat similarly, if an Rh negative woman carry the child of an Rh positive man and the embryo inherit an Rh gene from the father, the antibodies developed by the mother in response to the Rh factor in the fetus may pass into the circulation of the

child, clumping and destroying its red blood cells. The result is a disease called *erythroblastosis fetalis*, the most prominent sign of which is jaundice and the end often death either before or shortly after birth; fortunately it occurs in only one out of about 200 pregnancies. First-born children usually escape because, as after a transfusion, the antibody content of their blood does not rise high enough to exert any deleterious effect. But a second pregnancy may have the same outcome as a second transfusion, increasing this content to a point where it may be dangerous. It is obvious that a man and woman should know the Rh blood type of one another before entering into marriage.

The application of genetics to the protection and improvement of society is a complex and difficult problem, but given enough time the geneticist may succeed in solving it.

In any case, a prominent heart specialist of New York recently expressed the belief in conversation that the discovery of Gregor Johann Mendel may in the end prove to be even more valuable than William Withering's introduction of digitalis—a significant admission from one who must have relied so often on this sovereign remedy.

XIV

MILK SICKNESS

In the autumn of 1818, and in a rough unfinished log house at Pigeon Creek, Indiana, Nancy Hanks Lincoln, thirty-five-year-old wife of the unsuccessful Thomas and mother of Sarah and Abraham Lincoln, lay dying. Her sickbed was a crude affair of poles stuck between the logs in a corner of the cabin, whose floor was the ground under which she was so soon to lie. With one supreme effort she gathered all her resources and, fumbling at the boy's head as if in benediction, seemed to say in broken tones that he must grow up and be good to his sister and his father.

Returning for the moment to his former trade of carpenter and aided by Dennis Hanks, a small boy of the neighborhood, Thomas sawed out some rough boards from a black cherry log for her coffin and smoothed them with a plane. Nails there were none in that remote little settlement, so the nine-year-old Abe whittled out some wooden pegs with his jackknife to serve in their stead; then, while he and Dennis held the planks, Thomas bored holes into which the pegs were driven. In this rude case the body was borne to a wooded knoll about a quarter of a mile from the house and buried beside those of Mrs. Brooner, a neighbor, and Betsy and Thomas Sparrow, Nancy's aunt and uncle, all of whom had preceded her shortly before in death from the same cause.[5, 18] Not until some time later did an itinerant Baptist preacher visit Pigeon Creek and hold a service over their graves.

The cause of death in each case was milk sickness, a veritable scourge upon the settlers of the Middle West, which attacked both the pioneer and his domestic animals. Though it came almost universally to be called so once its origin in deleterious milk had been recognized, it had been known first as staggers, sick stomach, tires, stiff joints, puking fever, swamp sickness, river

sickness, or alkali poisoning—names all suggested by its symptoms or the source whence it was thought to be derived. In cattle it was called trembles.[19]

The date of its first appearance is not accurately known. It was said by some to have been mentioned, though in cattle only, by Bishop Hennepin, a French missionary who ascended the western rivers in the eighteenth century,[15] but others have denied that the writings of the good Father contain anything to warrant such a statement. In any case it certainly existed in North Carolina before 1776, and extended its range annually as civilization moved westward until it became prevalent in at least some parts of the Carolinas, the Virginias, Pennsylvania, Ohio, Indiana, Missouri, Arkansas, Wisconsin, Tennessee, Kentucky, Alabama, Mississippi, and Georgia; [26] often in river bottoms or timbered lowlands, along creeks, or near ponds. In Indiana it was spreading in 1819, in northern Missouri in 1823, and by 1825 it was only too familiar to settlers in most of the Middle West.

Milk sickness was a terrible disease, which made a more vivid impression on the pioneers than did any of the other plagues with which they were afflicted—and these included such formidable maladies as typhoid fever, Asiatic cholera, malaria, smallpox, and erysipelas, not to mention the infectious diseases of childhood.[23] Horses fell dead of it on the prairie, leaving the traveler to continue his journey on foot; cows dropped on the way from pasture to barnyard; whole villages were depopulated, and a rumor went abroad that the soil of Illinois was charged with death-dealing devils. Panic reigned. Immigration was halted for a space, and by 1836 the situation had become so discouraging as to elicit the dismal prophecy that some of the fairest regions of the West would remain forever a wilderness unless this hideous disease were conquered.[26]

"Go west, young man" may not have been such good advice after all.

An example of what milk sickness might do was offered by Dr. William J. Barbee out of his extensive experience with the disease. In the year 1838 a family of six persons traveling westward put up at a house a few miles east of Terre Haute, Indiana.

At breakfast they enjoyed liberal amounts of milk and butter, and immediately afterward went on their way. By the time they had reached Illinois, five or six hours later, they were all taken ill and died, every one of them, in from two to six days. Upon inquiry it was learned that the place where they had eaten their breakfast was in a "milk sick" region. No doubt it is presumptuous to question the diagnosis now; still, one cannot help asking whether the cause of death here may not have been food poisoning rather than milk sickness, which was apt to set in much more slowly.

Doctors found heartrending the sight of a family with from two to five of its members suffering at the same time.[14, 27] One declared milk sickness the most formidable difficulty with which he had to contend in Indiana,[22] and another wrote that in 1839 Danville, in the same state, had become a "perfect charnel house," no less than 50 persons in a population of 500 having died of it.[17] A single practitioner had seen from three hundred to five hundred cases during its highest prevalence.[31]

Nearly one quarter of the early settlers in Madison County, Ohio, were estimated to have died of milk sickness,[26] and around 1815 it was thought to have caused nearly half the deaths in Dubois County, Indiana.[17] The mortality was set by the physicians of the frontier at from 25 to 40 per cent, but it is believed to have been not over 10 per cent when all cases are included in the reckoning, mild ones never seen by a medical attendant together with the severe ones.[17] Nevertheless, a disease that kills one out of every ten victims is no laughing matter.

The actual mortality is impossible to discover. There were no vital statistics on the frontier, and prior to 1840 about three quarters of its physicians had been trained by the apprentice system, while even those who had been graduated from the small medical schools of the Middle West were still poorly educated; neither group, therefore, could have been expert in the diagnosis of their day, such as it was. On the other hand, those brought up in the better schools of the East were entirely unacquainted with milk sickness and inclined to doubt its very existence, regarding it as "a mere matter of credulous fancy." [26] Hence some of the

deaths ascribed to it by the former group may have been caused by food poisoning of one sort or another, while some referred by the latter to "gastritis" or to "ptomaine poisoning" may have been brought about by milk sickness. This seems to have been confused not infrequently, too, with what was called "typhus fever" at the time but was really typhoid fever, or occasionally even with malaria, with which it had little or nothing in common; the characteristic chills, for example, were not a feature of milk sickness. Finally, it was said in 1930 that dozens of deaths from milk sickness were reported every year as having been caused by diabetic coma, which it closely resembled in some respects, or by uremia or still other diseases. Not a single death from milk sickness had been recorded since 1920, though some had been mentioned in the newspapers. People objected strongly to the diagnosis because it decreased the value of their holdings, and whereas landowners would always admit that there had been cases higher up or lower down the river they would stoutly deny that there had been any in their immediate locality.[29]

Cream, cheese, and butter made from affected milk were soon found to be noxious as well, and it has been said that as small an amount of cream as ordinarily went into a cup of coffee had caused milk sickness. But if this be true the attack must have been a mild one, for the severity of the disease varied directly with the amount of milk consumed.

In speaking of transmission by dairy products, Dr. George B. Graff, of Illinois, wrote indignantly of a "murderous" practice in certain districts, where the inhabitants would not eat the butter and cheese made there "but with little solicitude for the lives or health of others, they send it in large quantities to be sold in . . . cities . . . particularly Louisville . . . and St. Louis. . . . Of the truth of this I am well apprized by actual observation, and I am as certain that it has often caused death in those cities, when the medical attendants viewed it as some anomalous form of disease, not suspecting the means by which poison had been conveyed among them."

By 1840 milk sickness was thought to be regressing somewhat,[31] but the decline was only apparent. In 1874 there was a

"regular epidemic" in Kenton, Ohio, where one physician alone had seen upward of thirty cases, and in 1892 it was said to be as prevalent in Tennessee as at any time in the preceding fifty years.[17] There were outbreaks here and there from 1907 to 1917, and four known ones in Illinois during 1936 and 1937, with twenty-one cases and two deaths.

The first written account of this sinister disease appears to be that of Daniel Drake, the great physician and teacher of the Middle West and one of the most picturesque figures in American medicine, who published a brief note in 1810. As he was a man of the cities he had to rely for his information on a country doctor who was familiar with milk sickness, since it occurred only in rural districts. At that time Drake did not regard the disease as a serious menace, but before long he had to change his opinion and he and other physicians began filling the medical journals of the day with descriptions of a blight that was actually delaying the settlement of the Middle West.

The premonitory sign was a characteristic and "indescribable fetor from the lungs," [15] which some writers on milk sickness did not emphasize enough or even neglected entirely, and knowledge of which would have prevented many errors in diagnosis had it been widely disseminated among the practitioners of medicine. When it was mentioned it was compared with the odor of garlic or of chloroform liniment; some called it sweetish, and an undertaker said it reminded him of the smell of rising milk bread or of salt-rising bread.[17] So distinctive was it that the inhabitants of an afflicted area insisted they could recognize the disorder in man or beast by the odor of the breath alone, and tanners professed themselves able to pick out by smell the hides of animals that had died of trembles. The odor was identified later as that of acetone.

After a few days patients began to say that they felt weak and had no appetite.[15] They grew uneasy; had difficulty in concentrating on anything and feared impending calamity, as well they might; they became irritable in temper, started at the slightest noise, sometimes complained of dizziness, ringing in the ears, intolerance to bright light, and muscular pains in the limbs or at

the nape of the neck, but not often of headache. Intractable vomiting set in next, followed shortly by an almost intolerable burning pain that was referred vaguely to the chest or the abdomen. As neither food nor water could be retained thirst was intense and exhaustion complete.

Now the tongue, white-coated at first, rapidly swelled to an inordinate size until it filled the mouth entirely, and it became so soft as to retain a perfect impression of the teeth. Considerable effort was required to protrude it for examination, and when after several trials the attempt had at last succeeded a tremulous motion was observed. Next to the odor of the breath this swelling of the tongue was the most typical sign of milk sickness. If the patient lived long enough the organ returned eventually to something like normal size, but its surface became glazed, dark, obstinately dry, and fissured.

The skin was cold, clammy, and of a yellowish hue; the cheeks were flushed, the lips unduly red, the eyes bloodshot and secreting. The temperature remained characteristically normal or subnormal throughout. In those who were to die the pulse grew rapid and irregular; drowsiness coupled with muscular twitching and a low muttering delirium set in, and convulsions and coma brought the scene to a close, usually from the second to the ninth day but occasionally not until three or four weeks had dragged by.

Patients who recovered from a severe attack required months, or often years, for restoration to full health, depending on the initial severity of the illness and Graff wondered, indeed, if they ever did recover entirely. Trembling or even prostration after exercise of any sort was a common feature of convalescence, and unusual exertion was sometimes followed by a relapse.

Besides the acute form just described, a subacute or chronic form called the "slows" was recognized. Its symptoms resembled those of the acute type, except that they were less severe. There were lassitude, vomiting spells, capricious appetite, stiffness of the legs with cramps in the muscles of the calves, emaciation, yellowish skin, and the odor of acetone on the breath. This condition might persist for months, interrupted by periods of seeming improvement, to be transformed at any moment by over-

exertion into the acute variety. Even in the chronic form the outlook was considered grave, and if the illness lasted weeks or months the patient was apt to die of heart failure or become permanently demented.

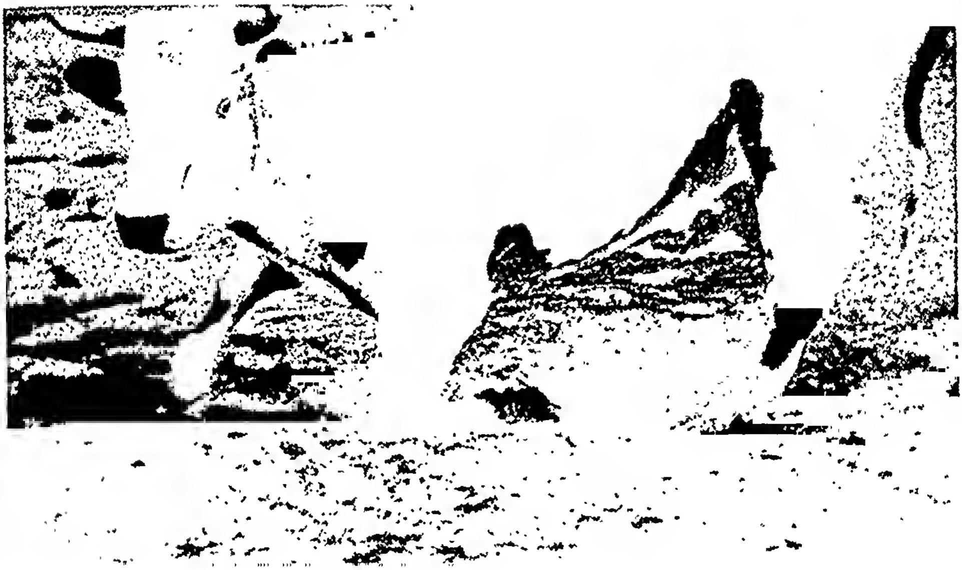
Milk sickness bit deeply into the lives and even affected the speech of Midwesterners. Thus Gideon Welles wrote in his diary that surprise was expressed at a Cabinet meeting when the hesitant General McClellan was ordered to take command of northern forces in Washington. Lincoln replied in effect that the General was well fitted to the task but that as he was troubled with the "slows" he was of no use in an onward movement.[1]

Transfer of milk sickness from one person to another had never been observed, yet even as late as 1914 there was still some doubt whether this evil disease was an infection or an intoxication. But those who considered it the former would have had to explain the subnormal temperature and the absence of a high leucocyte count.[6]

In cattle the first sign was muscular weakness. The victim began to falter in its gait and then to tremble, and because the disease in its earliest stages might pass unrecognized it was the custom of butchers to exercise any suspected animals vigorously before slaughtering them, in order to bring out this conclusive sign.[15] A physician wrote that on one occasion, puzzled by the illness in a family he had been called to attend, he went out and chased their cattle around the lot—a sight that one would not willingly have missed.

The trembling stage was followed by one of exhaustion, in which the animal sank to the ground, unable to rise, and often remained for hours or days on the spot where it had fallen until it either died or, in some cases, recovered.[17] As in man, the odor of acetone was almost overpowering.

In later years, acetone bodies were discovered in the blood and urine of human patients and lower animals with the disease, which was recognized accordingly as an acidosis or, more accurately, a decrease in the alkali reserve of the body, since the blood can never become really acid during life. Postmortem examination revealed extensive destruction of the liver, to which



THE TREMBLES

this decrease in alkali was secondary, and milk sickness and trembles were identified at last as a poisoning.

As for treatment, physicians were not easily consulted on the frontier; the nearest one was thirty-five miles distant from the Lincoln home, for example. Partly for this reason but partly, too, because even if he were called in the doctor was almost as helpless as the stricken family, many of the early settlers trusted to their own household remedies. Since the cause and the nature of milk sickness were both entirely unknown, the medical attendant could do little more than support the patient's strength as best he could and try to relieve the distress. But most of the measures employed were useless and some, like bleeding and the denial of water, positively harmful. Drake wrote that the people believed purgatives, enemas, tonics, and bleeding to be of uncertain value or no value at all and thought the most efficient remedy was blistering over the region of the stomach to allay the vomiting; wine and salted meat were said to be relished, he continued, and had appeared to do good. But it is hard for us to understand how a dehydrated patient whose body was crying for water could take, enjoy, and profit from salted meat. "Ardent spirits" were thought by some to make the disease worse—a lamentably wrong conclusion, as will shortly be seen.

Every doctor had his own favorite treatment and no less than eight different lines were employed in Ohio alone,[19] either singly or in combination, not to mention those used throughout the Midwest by the irregular "botanic" and "water-cure" practitioners who flourished there in pioneer days. But no internal remedy proved to be of real value. Physicians were inclined to consider bleeding the most useful measure provided it were undertaken early, for after a few days of illness the patient was too weak to stand it.[15]

Among the drugs hopefully tried were opium, calomel, castor oil, spirits of turpentine, senna, magnesium or sodium sulphate, Seidlitz powders, cream of tartar, jalap, lobelia, bismuth, hydrastis, strychnine, and digitalis. These are either narcotics, purgatives, tonics, or stimulants, and it is obvious at once that they

were given only in the hope of alleviation. The list recalls Osler's saying, that when many drugs are used in a disease none is of any value. A favorite domestic remedy, charcoal suspended in milk, may have been worse than valueless; really harmful, if the milk were still poisoned. External applications, in addition to blistering agents and cold water, included oil of peppermint or spearmint, and mustard plasters.

The best physician of them all was Dr. William M. Beach, who found that death rarely occurred when the administration of whisky was begun early enough in the disease and continued until convalescence had set in. He prescribed four ounces, well diluted with water, every four hours, and obviously it had to be started before vomiting had begun. Whisky had been given for years, perhaps as a household remedy, for it was a hard-drinking population; but patients had been denied the water they so desperately needed because sick animals that had tried to slake their thirst were often found dead beside a pond or a stream, and water was therefore considered inimical.

An old treatment with brandy and honey was even better than whisky alone, but it must have been either an inspiration or the result of trial and error, since the imperative need for both alcohol and sugar could not have been appreciated until the nature of the disease had been discovered.

The cause of milk sickness had been recognized in part before 1811, when an anonymous article in *Liberty Hall* ascribed it to some deleterious quality in milk and related the experiences of two farmers, Alexander Telford and Arthur Stewart, of Miami County, Ohio. The former said that observation and experiment during the preceding two years had left no doubt that poisoned milk was responsible, so that when he and his family were attacked he determined to stop using both milk and butter. Though the most violently affected member of the group, he was soon much better than any of them. When the family became too ill to milk their four cows the calves were allowed to take all the milk, and died within a week; thereupon his household discontinued the use of milk and began to get better, resuming it without harm

some weeks after the cows had been put into a cultivated pasture. One of his neighbors, he said, had pursued a similar plan with equal success. Some of his and Stewart's children vomited their milk regularly throughout the whole summer, when it was observed to have a peculiar taste and smell, and these suffered less than the other children. Neither Telford nor Stewart had ever seen milk sickness in persons who refrained entirely from the use of milk and its products. The anonymous author of this article suggested that the cause might be found by examining the stomach contents from cows dead of trembles.

Major S. H. Long, who traveled from Pittsburgh to the Rocky Mountains in 1819–20, had been told that at certain seasons of the year cows in northeastern Missouri gave milk that proved fatal when consumed, and that this property was attributed to a poisonous plant frequent in the low grounds, where it was eaten by cattle. Elsewhere he had been informed that the milk of cows running at large in August caused illness, "and this they . . . attribute to plants; and in some places they point out to you one and in other places another vegetable, to which they assign these properties. . . ."[26]

The problem had been solved except for identification of the guilty plant, yet precious time was lost and lives were needlessly sacrificed in arguments about the dew on the grass, a poisonous exhalation from swamps, the web of an innocent spider, animalcula, yeasts, impure soil, the bite of a certain fly, the seeds of a vegetable, an excess of carbon dioxide in the air, and minerals such as those of arsenic, copper, mercury, cobalt, barium, and aluminum.[25] A geologist drank water from every pool and spring in an affected region without suffering harm, and examined the water without finding any poisonous contaminant.[26]

Nevertheless, the majority of farmers, and of physicians as well, suspected most strongly some member of the vegetable kingdom. But which one was it? A dozen, more or less, were suggested at one time or another up to 1909, including white snakeroot, poison oak, Indian tobacco, Indian hemp, marsh marigold, poison sumac, wild "parsneps," and various mushrooms.[25]

Yet in 1839 John Rowe, a farmer of Fayette County, Ohio,

had published an article in an Ohio journal clearly implicating the white snakeroot! Refusing to accept any hypothesis that could not be proved, this neglected discoverer of the cause of milk sickness had fed extracts of the weed (then known as *Eupatorium ageratoides*, but now called *Eupatorium urticaefolium*) to a pig, two calves, two cows, and an ox, and the neighboring farmers who had been called in to witness the experiment identified the resulting disease as typical trembles.

Sixteen years later, in 1855, W. J. Vermilya, of Ashland County, Ohio, on whose farm trembles had broken out among the sheep, found his woods full of white snakeroot, fed it to animals, and killed two horses and several sheep thereby. Though he said that an article published earlier in the year by General Lucius V. Bierce had aroused his interest in the matter, he asserted later that he had solved the problem of trembles and evidently claimed a reward, for the corresponding secretary of the Ohio State Board of Agriculture, at a meeting on January 26, 1858, was instructed to thank Mr. Vermilya for his communication and inform him that it was the Kentucky, and not the Ohio, State Board of Agriculture that had offered a bounty for the discovery of the cause of the disease.

Finally, W. Jerry, a farmer of Madison County, Illinois, gathered on a June day of the year 1860 some plants that he believed harmless to be cooked for greens. His wife prepared them for the table, he tasted them and, noticing a peculiar odor and flavor, immediately suspected a mistake. None of the other members of his family ate any and all remained well, but the next day he was taken acutely ill with symptoms exactly resembling those of milk sickness. Recurrent attacks were experienced, and he did not recover entirely for five years. Later he administered a decoction of the weed, afterward identified as snakeroot, to a dog, which became violently ill in consequence.

Now the facts were more nearly complete; pigs, cattle, horses, sheep, a dog, and a man all given milk sickness either intentionally or inadvertently by snakeroot. Why did confusion persist? Through the great influence of Drake, who had regarded Rowe's evidence as inconclusive? [19] Or because of the primitive state of

communication and the relatively small number of medical journals? In 1867 a physician had reported an outbreak of milk sickness in which all the cases occurred in American families, who drank their milk raw, whereas German families, who boiled theirs, remained exempt, although the cows of both grazed on the same ground and had trembles.[17] Why did the news not travel by word of mouth, if by no other means? Among the medical men who wrote on milk sickness there were those who had had it themselves; why, in the face of such startling evidence?

The length of its sway is one of the most puzzling and tragic features of the disease. Ever since 1800 farmers had realized that it was an autumnal malady, most common from August on through October, and most likely to occur in hot, dry seasons, when grass was burned brown and cattle were turned loose to graze where they would and on whatever they could find.[6] At about the time of Rowe's announcement, in 1839, the white snakeroot, in full flower during the dangerous season, was strongly suspected by Kentucky farmers,[26] for although livestock did not like it they found its succulent green stems preferable to scorched grass. Certainly it fulfilled all the requirements. A perennial belonging to the composite family, it grows from July to November in the shade and thus withstands drought more successfully than most plants, proliferating luxuriantly in woods, swampy areas, shady ravines, and groves along watercourses, or exactly the places sought by cattle in the heat of a summer day. It attains a height of from one to four feet, or occasionally more, and flowers in September, bearing clusters of white blossoms; the leaves are tapering and coarsely toothed.[6]

Yet despite all evidence, and the appointment of committees in several states to investigate a disease that was killing valuable livestock by the thousand and destroying human lives as well, confusion was rife. While some physicians on the frontier were writing extensively on the subject and doing their utmost to solve the problem, others were denying that milk sickness was ever caused by dairy products or disputing its right to be called a separate disease.

It is a truism that any problem looks easy after it has been

solved, and no doubt this one was more difficult than it seems today. To begin with, the milk of affected cows that yet showed no sign of trembles was already poisonous, and sometimes the first warning that anything was amiss would be sudden and mysterious illness in a farmer's family. Thus instances were cited in which the disease appeared three weeks before a cow became noticeably sick. Secondly, snakeroot from different regions is now known to vary greatly in the ability to cause trembles, some samples being almost harmless whereas others are highly dangerous, and the danger increases with the amount eaten. Toxicity varies, too, according to whether the weed is fresh or dried, being higher by far in the green plant.[7] These comparatively recent discoveries would have answered in part, at least, the objection that if snakeroot really were the cause of trembles then all animals eating it should develop the disease, which was not the case.[25] Finally, cattle in the Southwest developed trembles in the absence of snakeroot, an argument that seemed valid until it was shown that the disorder can be elicited also by the rayless goldenrod, or jimmy weed (*Aplopappus heterophyllus*).[26]

Although a few of the early investigators, farmers and physicians in common, attacked the problem experimentally as best they could, feeding animals with snakeroot, heated or unheated dairy products and flesh from sick animals, giving mineral poisons or seeking them in water and soil, E. L. Moseley was the first to undertake a systematic study of trembles in accordance with modern laboratory standards. In 1905 he reported that he had produced it in cats and rabbits by feeding snakeroot or administering infusions of the weed. But A. C. Crawford, who carried out similar experiments, and actually drank an extract of the fresh plant without experiencing any of the symptoms of milk sickness, concluded that Moseley had not even proved snakeroot to be poisonous, much less the cause of trembles; and this despite the fact that four of his own thirteen tests gave positive results.

Then for a time it seemed that a bacillus, optimistically called *B. lactimorbi*, or the bacillus of milk sickness, might perhaps be

the long-sought cause,[17] and a similar disgrace was proposed for aluminum phosphate.[25] The tide turned again, however, and by 1917 several groups of investigators had published articles confirming the etiological role of snakeroot.

All the argument and uncertainty led Walter G. Sackett to renewed investigation of the subject. After a long series of careful experiments he came to the conclusion that the leaves of the white snakeroot contain something that is poisonous for rabbits, and present whether the plant be cultivated in the greenhouse or grown under natural conditions out-of-doors. But the toxic principle was not identified.

The final chapter in this long story of argument, error, superstition, observation, and experiment was written by Dr. James Fitton Couch, a chemist in the Pathological Division of the Bureau of Animal Industry, in Washington. He found that white snakeroot, or richweed, as it is sometimes called, contains three poisons, two of which do not cause trembles and so have nothing to do with milk sickness. The culprit is the third one, a thick, straw-colored, oily liquid with a pleasant odor reminiscent of clove or nutmeg, to which the name tremetol was given, from the Latin word *tremere*, to tremble. Present also in the rayless goldenrod, it has the characteristics of a secondary alcohol, and the formula $C_{16}H_{22}O_3$ was assigned to it. When administered to animals it elicited characteristic trembles. Carefully controlled experiments did not confirm earlier reports of transmission of the disease by feeding the flesh of affected animals, and Couch thought that tremetol does not accumulate there in amounts large enough to be dangerous, estimating that an animal would have to consume about half its body weight of meat before receiving a lethal dose. In any case, only raw meat would be dangerous for the poison is destroyed by boiling and naturally, therefore, by the even higher temperature of an oven. Pasteurization does not abolish it, however, for here the temperature is only from 131° to 158° F.

The nature of the poison in the milk was left an open question. As tremetol is a rather unstable compound it probably could not resist the chemical activities of the body and appear unaltered in

the milk, but was likely to be oxidized, a process that might entail no change in its toxicity; however, its ultimate fate was still unknown.

All the recorded cases of milk sickness have been in families that used their own dairy products, as did the Lincolns, and Couch thought there would be little danger in those from large distributors, for any contaminated milk would be diluted by mixing with that from other herds and the deleterious principle, whatever this might be, reduced below the toxic level.

From the standpoint of practical medicine the most important and interesting property of tremetol is the readiness with which it combines with ordinary alcohol to form a less poisonous compound. This explains the favorable effect of whisky, noted so long before the reason for it was known, and modern treatment includes the administration of alcohol in some form, even to the point of intoxication. Solutions of glucose are given intravenously to supply both water and a source of energy for the muscles, since the deficiency of this sugar in the blood was responsible for the extreme exhaustion in man and the muscular weakness in animals of which trembling was the first indication. Vigorous exercise used up this sugar rapidly, of course, and so brought out the characteristic sign.

Tremetol is a virulent and cumulative poison that attacks especially the liver, the kidneys, and the heart muscle whereas the brain and the rest of the nervous system, thought by earlier observers to bear the brunt of the assault in milk sickness, seem to escape. It was the extensive destruction of the liver that caused the fall in blood glucose, for one of the almost innumerable tasks of this jack-of-all-trades and master of all is to store the glycogen from which the glucose in the blood is renewed as occasion requires.

Supplementary to alcohol and glucose in treatment are the administration of water by rectum to complement that given intravenously as glucose solution, and the prescribing of alkalies in the hope of controlling the acidosis that results from damage to the liver and kidneys. Yet despite modern therapy many of the hor-

rors accompanying this loathsome disease had been encountered as recently as 1938 by Dr. J. S. Templeton. Fortunately it had become rare, he said, as had trembles, and only nine articles on it had appeared in the fifteen years preceding.

A search of the literature from 1938 to the present time revealed not a single reported case, so the situation seems to have improved still further. The clearing, drainage, and cultivation of land; the fencing in of pieces known to be dangerous; the rooting up and burning of the responsible weed; and the pasturing of stock on the farm instead of at large have all contributed to the conquest.[14] No one need ever write again, as did one of the early settlers: ". . . we war perplext by a Disese cald Milk Sick." [19]

But all these preventive measures had long been known, and if the experience of farmers had been taken more seriously, and their advice heeded, ruinous losses in livestock could have been prevented and thousands of human lives saved.

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